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CHOLEDOCHOENTEROSTOMY IN CHRONIC RELAPSING PANCREATITIS*

A Study of Five Cases with Prolonged Follow-up Observation

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THE management of pancreatitis in the chronic phase is a vexatious problem, particularly in the stage variously referred to as chronic relapsing pancreatitis, acute recurrent pancreatitis and subacute pancreatitis. The medical or nonoperative prevention of recurrences of acute pancreatitis has been difficult to evaluate, but seems ineffectual in most cases. The surgical approach, in general, is also unsatisfactory, as attested by the many varied procedures that have been advocated at different clinics. Chronic atrophic pancreatitis is an equally difficult problem for medical or surgical management, digestive and metabolic disturbances and pain being the symptoms most characteristic of this late stage of the disease.

In 1948 Doubilet and Mulholland[1, 2] reported beneficial results in cases of pancreatitis treated by surgical division of the sphincter of Oddi. At that time, and subsequently, they were impressed with their favorable results.[1-6] More recently, Bowers[7, 8] has studied the results in 11 cases of pancreatitis (6 of these have been reported) treated by choledochojejunostomy, a defunctionalized limb of jejunum being employed for the choledochoenterostomy.

The rationale of both the surgical approaches lies in the common-channel hypothesis for the etiology of pancreatitis, based in great part on the classic studies of Opie[9] and Archibald.[10] However, we agree with others that certain anatomic and physiologic observations, made both in the laboratory and clinically, militate against the general acceptance of the common-channel theory. Most of these objections have never been successfully refuted.

A pilot study was planned and initiated in a small number of cases of pancreatitis. In 4 cases of well documented chronic pancreatitis, in which the diagnosis was substantiated at operation, choledochojejunostomy was performed exactly as recommended by Bowers.[7] An additional case, in which the diagnosis of pancreatitis was consistent with the clinical picture but was not corroborated by the pathological findings at the time of operation, is included in this series.

We elected to do the more complicated operation of choledochojejunostomy rather than sphincterotomy for the following reasons:

Complete separation between biliary and pancreatitic secretions is assured by this procedure. Therefore, the effect of choledochoenterostomy on the course of chronic pancreatitis represented a more rigid test of the therapeutic application of the common-channel hypothesis. Failure to cure the disease could not be attributable to incomplete section of the sphincter, to regeneration of the sphincter or to the pinch-cock effect of the duodenal musculature on the distal common duct, which could reproduce the action of the sphincter.

The danger of postoperative cholangitis seemed less if the common duct were anastomosed to the defunctionalized limb of bowel than if it were left patulous and exposed to the alimentary stream, as after sphincterotomy, as suggested by Gray.[11]

Since the initial reports by Doubilet and Bowers, other cases of pancreatitis have occasionally been treated with sphincterotomy, or with choledochoenterostomy or cholecystoenterostomy by other surgeons.[12-17] Contrariwise, several other papers have been presented during this time supporting other methods of treatment, and inferentially disagreeing with the principle of a common channel.[18-22] We are not aware of any complete report after these procedures, designed to prevent a confluence of biliary and pancreatic secretion, in which the poor results were at least as frequent as the good results.

We have therefore considered it of some importance to report our experience in a small number of patients subjected to choledochoenterostomy for chronic pancreatitis and followed carefully for three years or more after choledochojejunostomy;

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the results are unsatisfactory. This lack of success with a procedure that seems to be gaining limited recognition in surgical circles indicated the need of presenting our experience with a small though carefully studied group.

Case Reports

Case 1. T. Z. (S.V.H. C35594), a 49-year-old man, had a diagnosis of chronic pancreatitis because of recurrent bouts of abdominal pain, vomiting, weight loss and persistent diarrhea after cholecystectomy for acute cholecystitis on September 17, 1949. At operation no mention was made of the condition of the pancreas. There were no calculi in the gall bladder or common duct. In addition, during the period of observation, pancreatic calcinosis developed, and there was evidence of poor pancreatic function as measured by deficient pancreatic secretion and poor digestion of fat and protein. Choledochojejunostomy was performed on April 14, 1950. The pancreas appeared grossly atrophic and nodular, and was o e fourth the normal size. Histologic examination of a pancreatic biopsy specimen demonstrated increase of the intralobular fat, and hypoplasia of the acinar tissue, with increased fibrous tissue in the interlobular septums. The postoperative course was uneventful. The patient was readmitted 2 months after operation for a cholangiogram and removal of the T tube. Diarrhea and abdominal pain were diminished immediately after operation, but 5 months later both these symptoms returned. He was followed for 24 months after the choledochojejunostomy, with no improvement in abdominal pain, diarrhea or state of nutrition.

Case 2. A. A. (S.V.H. C26854), a 33-year-old man, had a diagnosis of relapsing pancreatitis because of recurrent upper abdominal pain radiating to the back and shoulders of 9 years' duration. The pain was accompanied by nausea, vomiting, high temperature, chills and tenderness in the upper part of the abdomen. He had 6 admissions for these complaints and was exhaustively studied, no definite diagnosis being arrived at until 2 elevated serum amylase determinations were obtained during an acute attack. During one of these admissions, on December 4, 1941, cholecystectomy was performed. No calculi were present in the gall bladder or common duct. The status of the pancreas was not noted. The gall bladder showed atrophic changes but no inflammation histologically.

On May 3, 1950, a choledochojejunostomy was performed. Unfortunately, a biopsy of the pancreas was not taken. Two months later the patient was admitted to the hospital for a cholangiogram and removal of T tube.

He has had 5 hospital admissions because of pain in the upper abdomen 6, 25, 29, 30 and 39 months since operation. In addition minor episodes of epigastric pain have frequently necessitated absence from work for several days.

Case 3. A.T.E. (S.V.H. C31990), a 33-year-old alcoholic Negress, had a diagnosis of chronic pancreatitis because of recurrent episodes of abdominal pain after the demonstration of pancreatic edema and fat necrosis at the time of cholecystectomy on May 29, 1949, for noncalculous acute cholecystitis. Pancreatic secretions were normal; the serum amylase was elevated on one occasion. On April 27, 1950, choledochojejunostomy was performed. The pancreas was extremely hard. There were areas of recent fatty necrosis, and calcified sites of older necroses were noted. Histologic examination of the pancreatic biopsy specimen demonstrated marked increase in interlobular connective tissue and an intense infiltration with lymphocytes. Two months after operation, the patient was readmitted for cholangiogram and removal of the T tube. Since choledochojejunostomy she has been readmitted to the hospital on two occasions with similar complaints, evidence of upper abdominal peritonitis and elevated amylase determinations. She has lost 86 pounds in the 37 months since operation. In addition to severe acute exacerbations, she has almost constant upper abdominal pain.

Case 4. K.P. (S.V.H. C40329), a 37-year-old, married woman, was admitted to the hospital for investigation of repeated attacks of right-upper-quadrant pain of 10 months' duration. The pain, which was knifelike and high in the epigastrium, radiated to the back, and the more severe attacks were accompanied by nausea and vomiting. There was no relation to food intake. The patient had never been jaundiced. No stool abnormality or change in bowel habits had been noted. There were periods in which she was asymptomatic for as long as 2 or 3 weeks. The past history was significant in that in 1939 she had had an episode of similar pain. In 1949 she had another episode of right-upper-quadrant pain, and cholecystectomy was performed at another hospital for noncalculous cholecystitis. No mention was made of the status of the pancreas. Pain had recurred 4 months after operation, continuing intermittently until admission.

Physical examination showed epigastric tenderness (the patient was admitted during a remission of symptoms). She weighed 113 pounds. The temperature was 99.2°F.

The serum amylase was normal. Pancreatic secretion, as measured in duodenal drainage, was greatly decreased in volume (60 cc. per hour). Enzyme content was also low. X-ray studies of the intestinal tract demonstrated no other disease.

The diagnosis of chronic pancreatitis was made, on the basis of suggestive history and diminished duodenal enzymes. Choledochojejunostomy was performed on May 9, 1950. The pancreas appeared grossly normal. At discharge, the symptoms were relieved. The T tube was removed 9 weeks later. Symptoms recurred shortly afterward and, 2 years later, had become so severe that bilateral sympathectomy was performed, consisting of removal of the 11th and 12th thoracic and the first lumbar ganglions. This only resulted in unilateral ablation of pain, the pain pattern recurring on one side.

Case 5. A. G. (S.V.H. C 42391), a 53-year-old woman, had a diagnosis of recurrent pancreatitis because of recurrent upper abdominal pain, signs of peritonitis and markedly elevated serum amylase determinations (1400 and 241 Somogyi units) in the absence of cholangiographic evidence of gall-bladder disease.

On September 22, 1950, choledochojejunostomy was performed. The common duct was distended and thickened. The gall bladder presented gross evidence of cholesterosis, confirmed histologically. The pancreas was normal on gross examination, and biopsy showed no abnormal change. The patient was readmitted 2 months after operation for a cholangiogram and removal of the T tube. She has been asymptomatic during the 36 months since operation.

Analysis of Cases

In 5 patients with chronic pancreatitis choledochojejunostomy was performed, the technic described by Bowers[7] being used (Table 1). In no case was there a serious postoperative complication. The common duct was drained through a T tube in all cases for nine weeks after operation. Careful long-term follow-up study with personal examination was carried out. This period exceeded or equaled three years in all cases but 1. The results are shown in Table 1.

Table 1. *Results of Choledochojejunostomy in 5 Cases.*

Case No.	Operation	Condition of Pancreas	Follow-up Period	Result
1	Cholecystectomy in Nov., 1949; choledochojejunostomy in Apr., 1950.	¼ normal size & nodular, with increased interlobular fat	24 mo.*	Poor
2	Cholecystectomy in Dec., 1941; choledochojejunostomy in May, 1950.	Stony hard (biopsy not taken)	36 mo.	Poor
3	Cholecystectomy in May, 1949; choledochojejunostomy in Apr., 1950.	Stony hard, with increased interlobular connective tissue & lymphocytic infiltration	36 mo.	Poor
4	Cholecystectomy in 1949; choledochojejunostomy in May, 1950.	Normal on gross examination (biopsy not taken)	36 mo.	Poor
5	Cholecystectomy and choledochojejunostomy in Nov., 1950	Normal on gross and microscopical examination	33 mo.	Good

*Patient subsequently lost to follow-up study.

One satisfactory result is recorded. Case 5 has been totally asymptomatic since operation and

has been completely rehabilitated. A reservation must be made regarding this case. This patient had attacks of relapsing pancreatitis, as evidenced by high amylase determinations, with accompanying upper abdominal pain and signs of peritonitis. However, although the gall bladder appeared grossly normal at operation, pathological examination revealed the classic picture of cholesterosis. Preoperatively, as was expected with cholesterosis, the cholecystogram was repeatedly normal. Since the surgical procedure consisted of cholecystectomy, temporary choledochostomy and choledochojejunostomy, it is not reasonable to attribute the benefit of surgery to the choledochojejunostomy alone, particularly since cholesterosis was present.

Case 4 represents a failure of choledochojejunostomy to relieve the patient of symptoms. Some doubt may properly be cast on the diagnosis of pancreatitis. The clinical impression of chronic pancreatitis was borne out to some degree by the diminished pancreatic function. At operation, however, the pancreas was grossly normal, and a spontaneous rise in amylase did not accompany pain at any time. In this respect, it is only fair to say that the patient was not hospitalized when the majority of the severe attacks occurred, and there was no opportunity to study the serum enzyme content during an acute attack.

Discussion

This short series of cases suggests that separation of pancreatic and biliary flow does not always cure chronic relapsing pancreatitis. This conclusion is at variance with the reported experience of other surgical clinics, which have utilized choledochojejunostomy or sphincterotomy in the treatment of pancreatitis.

A review of the recent publications on the management of chronic pancreatitis by sphincterotomy and choledochojejunostomy is somewhat disturbing. It is difficult to compare and evaluate thoroughly the results obtained, though an initially favorable impression is gained for the most part. An important source of confusion is the well recognized difficulty in the diagnosis of the chronic stages of pancreatitis, particularly in recurrent acute pancreatitis, and to a lesser degree in that of chronic atrophic pancreatitis. It is generally recognized that this disease can probably elude diagnosis by the most thorough investigations and even defy tissue diagnosis, whether by gross inspection at operation or by histologic examination in the laboratory. In spite of this, it behooves one, when evaluating a new procedure in any disease, to lay down certain objective diagnostic criteria that must be fulfilled before the diagnosis is made. This is especially true of a process that can be as deceiving as pancreatitis. We, therefore, submit the following criteria, and believe that they are sufficiently rigid to provide an accurate diagnosis in nearly all cases of pancreatitis.

First, repeated bouts of abdominal pain, accompanied by significant spontaneous elevations of amylase and lipase content in serum or urine or both. It must be emphasized that one bout of pancreatitis does not signify that chronic relapsing pancreatitis is present, and more than one such attack is essential before relapsing, or chronic, pancreatitis can be said to exist. It is becoming increasingly obvious, in our experience and that of others, that a large, but determinable, number of initial attacks of pancreatitis are followed by no sequelae, or at least by a prolonged asymptomatic period. This is particularly so when the pancreatitis accompanies cholelithiasis and cholecystitis, and when adequate gall-bladder surgery is carried out. To the best of our knowledge, the significance of this has only been noted, in brief, in one report.[12]*

Secondly, demonstration of pancreatitis at operation by fat necrosis, edema of the gland, cyst formation and biopsy evidence of acute or chronic inflammation. When the typical clinical symptoms, in recurring fashion, precede or follow the organic demonstration of the disease, one can safely assume that chronic relapsing pancreatitis is present. Hardening of the gland alone, without atrophy or enlargement, cannot be considered evidence of chronic pancreatitis, unless clinical manifestations have been accompanied by rises in pancreatic enzyme content in the urine and serum. Everyone is aware of the residual marked hardening of the pancreas noted in the presence of duodenal and gastric ulcerations, whether active or inactive. Indeed, in routine palpation of the gland during laparotomies for other conditions, one is often struck by the marked variation in the gross characteristics that, without apparent symptomatology, are noted in this organ.

Finally, symptoms accompanied by one or more of the following manifestations point to the diagnosis of chronic atrophic pancreatitis, even in the absence of elevated serum enzyme content: alteration in carbohydrate metabolism or fat digestion; demonstration of pancreatic calcification on x-ray study; and repeated, and significantly low, pancreatic secretion, as demonstrated by duodenal drainage.

Unfortunately, some cases of pancreatitis can exist without most of these overt manifestations. Our contention is that failure to insist on some such criteria will lead to the confusion of pancreatitis with other ill defined conditions like "mucous colitis," "nontropical sprue," "duodenitis," "post-

*Since this paper was submitted for publication Raker and Bartlett[12a] have considered this subject at greater length.

cholecystectomy syndrome," "biliary dyskinesia," "abdominal epilepsy," "prolapse of gastric mucosa into the duodenum" and "psychogenic syndrome," and incorrect diagnosis, of course, will inevitably lead to a poor evaluation of any method of treatment applicable to "pancreatitis."

Our insistence on the pathological demonstration of disease in the pancreas grossly, and preferably microscopically, might seem to be too stringent, in view of the fact that pancreatic edema has been produced repeatedly in animals without detectable residual morphologic changes.[28] Nevertheless, it is unlikely that massive pancreatic damage, or the repeated injury to the pancreas of any degree, will not leave some residual anatomic stigmas. More important than any set of criteria adopted for the diagnosis of the disease is a clear elucidation of the diagnostic procedure used by the particular observer, so that comparison can be made with the work of other investigators.

We have utilized the criteria referred to above in evaluating published series of pancreatitis treated by sphincterotomy and choledochojejunostomy. Sphincterotomy has been strongly advocated by Doubilet and Mulholland,[6] who, in 1952, had performed sphincterotomy in 52 cases of suspected pancreatitis. Sufficient data for analysis are furnished in the series of 21 cases recorded in 1948.[1] The average follow-up period in these cases, until the time of publication, was five and eight-tenths months; the longest was fourteen, and the shortest three months. In 11 of these 21 cases observation of the patients postoperatively was limited to four months or less. Pancreatitis, in its chronic phase, is notoriously capricious in its asymptomatic periodicity and recrudescence. This allows only limited conclusions about the result of the procedure in these cases up to that time. This is certainly so when one considers that in the Doubilet–Mulholland series, the average duration of symptoms before operation was seven and one-tenth years, the longest period sometimes being twenty-two years, and the shortest three months. A most important consideration in the evaluation of this series is that cholecystectomy was performed in conjunction with sphincterotomy in 9 cases. In addition, in all of these cases, choledochostomy and drainage of the common duct was carried out for an undetermined period. This adds two variables that are difficult to evaluate, since chronic relapsing pancreatitis is favorably affected in many cases by removal of the gall bladder, and certainly temporarily by prolonged drainage of the common duct.[12] Gambill et al.[12] mention an asymptomatic period of four years after choledochostomy in a patient with pancreatitis.

Some doubt concerning the diagnosis of chronic relapsing pancreatitis arises in some of the cases presented in the Doubilet–Mulholland series. A total of 7 determinations of serum amylase are recorded, 2 of which, in the series of 21 patients, were within the normal range. More than 1 determination was not carried out in any patient. Decreased pancreatic function, as noted by duodenal drainage, is advanced as evidence of chronic relapsing pancreatitis in 10 patients. We have found this test to be useful only in the presence of repeatedly low determinations, since abnormally low pancreatic enzymes, even in the presence of a normal gland, are frequently obtained in a single duodenal drainage, unless the most diligent care is applied to prevent gastric contamination.

Of the 18 cases in which the condition of the pancreas at operation is mentioned, 5 are said to appear normal grossly. In 13 cases gross evidence of the disease was present, as suggested by "firmness," "hardness," "enlargement" and "nodularity" of the gland. These criteria for anatomic pancreatic disease are only of value when corroborated by such findings as fatty necrosis, pancreatic edema at a previous operation or one or more increased amylase determinations in association with the recurrence of pain. In none of the patients in this series was histologic examination made. Fatty necrosis was not noted in any case at the time of a previous laparotomy. In 1950 Doubilet and Mulholland[5] presented 4 cases of pancreatitis accompanied by calcification in which the immediate follow-up study demonstrated improvement, as evidenced by weight gain and general well-being. Three of the 4 were previously presented in the series of 21 cases just discussed, and these 3 represent the longest follow-up period in the experience of these authors. However, it is well to mention that, though pancreatic calcification is often a sequela of pancreatitis, it is not unusual to find cases of pancreatic calcification with no history of clinical pancreatitis in patients who are asymptomatic at the time of observation. In short, calcification per se is not an index of the chronicity or the activity of the disease.

A recent brief report on 23 cases of pancreatitis, treated by transduodenal sphincterotomy has been presented by Major and Ottenheimer.[14] Favorable results are noted in 20 cases. The shortness of the follow-up period makes it impossible for one to draw far-reaching conclusions; 82 per cent of the patients were followed for less than two years, and a little more than half for less than one year. The evidence on which a diagnosis of pancreatitis is made is tenuous. A high serum amylase is reported in 35 per cent of the cases, no repeated elevations being reported. In 48 per cent the pancreas was considered abnormal — that is, it showed edema, induration or fat necrosis, or there was a positive histologic examination. Of these criteria, we believe that only the last two are significant, unless accompanied by elevated amylases or a classic history and clinical pictures. An important point is that 52 per cent of the patients had cholelithiasis, and cholecystectomy was performed in 16 cases at the time of sphincterotomy. One speculates how many

of the patients with reported elevated amylases, or pancreatic changes, were also those with cholecystitis and lithiasis. A single episode of pancreatitis, when accompanying cholelithiasis or cholesterosis, although suggestive does not establish the diagnosis of chronic relapsing pancreatitis, and of this former group only a small percentage will have further difficulty after gall-bladder surgery. Curiously enough, in 2 cases, a calculus at the ampulla of Vater was considered a diagnostic sign of chronic pancreatitis. In these cases it seems that simple removal of the calculi would suffice, and that sphincterotomy would be superfluous. Major and Ottenheimer also adduce a tight sphincter as evidence of pancreatitis, as demonstrated by the difficulty in passing instruments from the common duct into the duodenum. In view of the labyrinthine distortion of the common duct, duodenum and pancreas during surgical exploration, any difficulty that may be encountered at the time cannot necessarily be ascribed to a "tight sphincter." This disputed point is further emphasized in a recent editorial[24] tempering the unopposed enthusiasm for sphincterotomy implied in the report of Major and Ottenheimer.

In addition to the large number of sphincterotomies performed by Doubilet and Mulholland and by Major and Ottenheimer, several surgeons have mentioned successful application of this operation in occasional cases.[13, 17]

Choledochojejunostomy, as advocated by Bowers,[7,8] has not been as extensively used. In 1951 he reported 6 cases with uniformly satisfactory results. In 1952 he had performed the operation in 11 cases, with satisfactory results in 9, and the follow-up period in 6 of the cases was at least two years. Bowers emphasized the importance of the occurrence of recurrent bouts of pancreatitis in the diagnosis of these cases, and the pathologic lesions were demonstrated histologically.

Poth[16] has briefly reported good results in 4 cases of cholecystojejunostomy and 1 of choledochojejunostomy, the longest follow-up period being two and a half years.

Bowers's cases are fully documented, and his diagnostic criteria guarantee the accuracy of the diagnosis. It is therefore difficult to explain our success in only 1 of the 5 cases in which essentially the same diagnostic criteria were used and the same operative procedure was carried out. An explanation of the divergent results may lie in the theoretical consideration that pancreatitis does not have the same pathogenesis in all cases. This assumption warrants a brief review and analysis of the implied postulates.

The common-duct theory comprises several basic postulates. There is no agreement about the actual anatomic confluence of the common bile duct and the pancreatic duct at the ampulla of Vater, proximal to the sphincter of Oddi. Cholangiographic studies have shown that in a fair percentage of cases of gall-bladder disease, opaque dye injected into the biliary tree enters the pancreas. In this respect it is interesting that in the Doubilet–Mulholland studies the phenomenon of reflux persisted in 11 of 15 cases after sphincterotomy.[4]

If this is so and if the disease is believed to be due to biliary reflux, sphincterotomy cannot be expected to alter the pathogenesis. A second assumption of the common-channel theory is that obstruction at the ampulla of Vater is present. Organic obstructions, such as calculi and mucous plugs, are rare. Schmeiden and Sebening[21] found 57 cases of papillary stones in 1278 cases of pancreatitis. Spasm of the sphincter of Oddi is then postulated as a cause of obstruction, although the spasm, whose pathogenesis is nebulous, has not been demonstrated experimentally. Studies to elucidate this mechanism, have not been well controlled, and have only been carried out in 1 or 2 cases.[2, 25] If one admits that there is a confluence of the pancreatic and common ducts and that the sphincter of Oddi, stimulated by some undefined mechanism, can produce obstruction of these systems, it does not necessarily follow that bile will flow into the pancreas. Clinical observations and experimental work suggest that pancreatic secretions are perhaps more likely to pass into the biliary system.[26, 27] Furthermore, bile is not essential for the production of pancreatitis.[26, 28] It is generally agreed that the rupture of the pancreatic radicles is a sine qua non if pancreatitis is to be produced by injection of the pancreatic duct.[28] It is difficult to conceive of a pressure sufficient to rupture the acini that can be generated under clinical conditions in a common biliary-pancreatic system. Fine[29] found that with the injection of bile at a pressure of 450 to 600 mm. of mercury rupture of the pancreatic ductules occurred, with production of hemorrhagic pancreatitis. Moreover, the sphincter of Oddi would probably give way first under this pressure. Doubilet and Mulholland[3] found the normal sphincteric resistance to be about 150 mm. of water, which rose to about 300 mm. after spasm induced by morphine.

Summary

Five cases of chronic relapsing pancreatitis treated by choledochojejunostomy are reported, with only 1 good result (in this case cholecystectomy for previously undiagnosed cholesterosis accompanied the procedure). To the best of our knowledge this is the first negative report, supported by documentary clinical evidence, with a long follow-up period.

Criteria for the diagnosis of chronic relapsing pancreatitis are presented.

Three series of cases treated by choledochojejunostomy and sphincterotomy are evaluated.

Failure of operations dividing biliary and pancreatic flows is considered suggestive evidence

against the common channel theory of pancreatitis operating in all cases of pancreatitis.

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A HEREDITARY FACTOR IN CHONDRODYSTROPHIA CALCIFICANS CONGENITA*

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CHONDRODYSTROPHIA calcificans congenita is a rare congenital condition diagnosed by the radiologic demonstration of multiple punctate calcific epiphysial deposits in an infant who may also have one or more of a variety of other defects. The observation of this rare disease in 2 siblings led us to consider the possibility that it was hereditary, and an analysis of the available family data in the literature was therefore undertaken from this point of view.

Characteristics

The disease was first described by Conradi,[1] who considered it a form of chondrodystrophia fetalis hypoplastica. It was named chondrodystrophia calcificans congenita by Hünermann[2] and has since been described under several other names, including dysplasia epiphysialis punctata,[3-5] chondrodystrophia fetalis calcarea,[6] chondroangiopathia calcarea seu punctata[7, 8] and congenital stippled epiphyses.[9] The incidence is estimated as 1:500,000 births.[10]

Radiologic Appearance

According to the reviews of Fairbank[3] and Putschar[11] the calcified epiphysial foci are small, discrete, and variable in size, number and location. They occur most frequently in the epiphyses of the long bones and cartilaginous tarsal and carpal bones, but have also been described in the patella, acetabulum, ilium, pubis, sacral wings, vertebras, ribs, cartilaginous portions of the skull and tracheal cartilages. Swoboda[12] has reported a case in which the deposits appeared only in the talus. In a few cases the calcific deposits have been shown to increase in number in the early postnatal period, but in patients surviving infancy the foci decrease in number and size, and eventually disappear. The diaphyses of the long bones may be short and thick, with splayed ends, and the epiphyses and metaphyses may be enlarged.

Associated Defects

Associated defects are frequently present. The most characteristic of these is shortening of the limbs, which is most pronounced in the proximal segments and sometimes occurs unilaterally, or in only one extremity. Flexion contractures, particularly of the hips, knees and elbows, with limitation of movement, are often seen. Other skeletal defects such as clubfoot and dislocated hips are occasionally present. The head is often large, and the bridge of the nose depressed.

Bilateral congenital cataracts have been described in a number of cases,[3-5, 9, 13-17] and congenital defects of the heart[17-19] and mental deficiency[5, 20] occasionally occur. Skin lesions, mentioned by several

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authors, have been identified by Curth[21] as those of follicular atrophoderma.

Biochemical Changes

Abnormal values have occasionally been observed on biochemical examinations of the blood, including an elevated concentration of blood calcium in the neonatal period[22] and an elevated value for serum phosphatase.[17] On the other hand several authors have reported normal values for serum calcium, phosphorus and alkaline phosphatase,[5, 10, 23] but no biochemical aberrations have occurred frequently enough to be considered characteristic of the disease.

Pathological Characteristics

Putschar[11] has reviewed the pathological studies and contributed his own observations on an infant with chondrodystrophia calcificans congenita who died at the age of twenty days. Histologic examination of the patella demonstrated areas of mucoid degeneration of the ground substance, with no evidence of calcification and no blood vessels in the degenerating areas. Other areas showed homogeneous calcification of ground substance. In places where vascular marrow channels adjoined the calcified areas there was proliferation of blood vessels and connective tissue, forming foci of cellular mesenchymal tissue that sometimes contained central areas where fibrous primitive bone was formed. Harris,[24] on post-mortem examination of a patient who died at seven months of age, found in addition to mucoid degeneration, a patchy irregularity in orientation of the cartilage cells similar to that found in achondroplasia. Hässler and Schallock[10] described calcification of perichondrial and subsynovial tissue of the knee as well as changes similar to those described above.

Prognosis

In most of the reported cases of chondrodystrophia calcificans congenita the child has failed to thrive, and in about half the cases death has occurred within the first year of life. If the patient survives the infantile period the calcific lesions tend to disappear and the child may be left with only a slight stunting of growth and the remnant of any asymmetry that may have been present in early life.[2, 10, 12, 17, 23, 25]

Case Reports

Case 1. R., a male infant and the 1st child of healthy, unrelated parents, was born on January 28, 1946.

A maternal aunt had a tetralogy of Fallot, but no other relatives with congenital defects were known to the parents. The mother, in particular, had no history or clinical signs of hyperparathyroidism or other metabolic disorder, and no evidence of any skeletal defect on thorough radiologic examination. Measurements of her serum calcium, phosphorus and alkaline phosphatase were within normal limits — calcium of 9.2 and phosphorus of 4.71 mg. per 100 cc. and phosphatase of 1.2 millimols per liter (nitrophenyl phosphate method).

Pregnancy and labor were normal. At birth the infant breathed and cried spontaneously; the nutritional state was fairly good, and there was no cyanosis. The facies suggested marked cerebral retardation. There was decreased activity, and a whining, high-pitched cry. The circumference of the head was 31 cm. The skull was high domed, with what appeared to be some premature synostosis of the sutures; the anterior fontanelle did not give evidence of increased tension. The heart, lungs and abdomen presented no abnormalities, but on examination of the extremities it was noted that the femurs and humeri were markedly shortened, the distal portions of the limbs being disproportionately long. There was outward bowing of the tibias and bilateral talipes calcaneo valgus deformity. The clinical diagnosis was atypical achondroplastic dwarfism with cerebral retardation.

X-ray examination on January 30, 1946, demonstrated fragmentary ossification of the cranial bones, particularly of the parietal bones (Fig. 1). A dorsolumbar kyphosis was present. The humeri were short, with broadened metaphyses. Their proximal and distal epiphyses and associated metaphyses presented gross bulbous masses containing fragmentary deposits of calcific material almost stippled in their distribution. A somewhat similar appearance was present in the femurs, being more pronounced proximally than distally, again with shortness of the diaphyses. There were lesser changes in the tibia on each side and relatively long fibulas. There were also calcareous deposits in the region of the patella, especially on the right side.

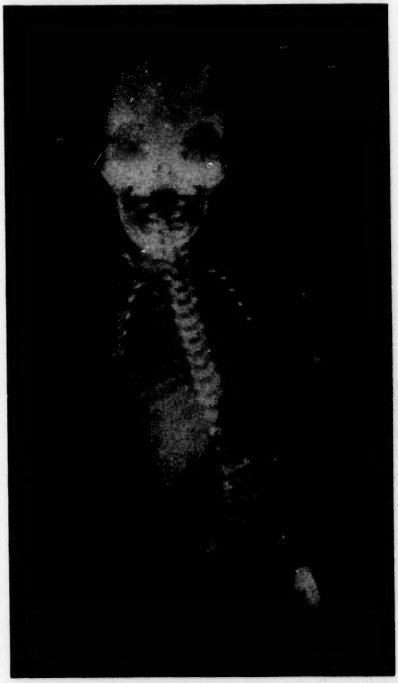

Figure 1. *X-Ray Film in Case 1.*

The patient never fed well; his condition gradually deteriorated, and he died at 3½ weeks of age. At autopsy the only abnormal findings were in the skeletal system and were compatible with those described by previous workers as occurring in this disease.

Case 2. The 2d child in this family was born in 1948, a normal female infant whose physical and mental development has fol-

lowed accepted standards. Radiologic examination of the skeleton at the age of 4 years showed no abnormality.

CASE 3. The 3d child, a female infant born on February 17, 1952, 2 weeks overdue, with precipitate delivery, presented several congenital abnormalities. The circumference of the head was 32 cm.; the face was asymmetrical, and the neck was short. The proximal segments of all extremities were very short, with flexion contractures of the wrists and knees. The facies suggested mental retardation, but the patient sucked well. The heart sounds were not abnormal at birth, but several days later

FIGURE 2. *X-Ray Film in Case 2.*

a harsh systolic murmur was heard over the precordium and transmitted to the back.

X-ray films of the entire skeleton showed symmetrical calcification of the secondary and some primary ossification centers in the upper and lower extremities, cervical and dorsal spine, sacrum and ischii (Fig. 2). The changes were most marked in the root bones of the extremities, where they were associated with symmetrical dystrophic deformities with marked shortening, widening and splaying of the ends of the humeri, moderate shortening and widening of the femurs, and minimal changes in the size and contour of the cervical, dorsal and lumbar vertebras. The calcification also affected some of the soft tissues related to the secondary centers, particularly about the knees. These changes were all characteristic of chondrodystrophia calcificans congenita. There was an associated microcrania of moderate degree that presumably was due to microencephalia.

The infant did not do well, taking very little food, and her condition gradually deteriorated until she died at 3 weeks of age. Since death occurred some distance from the city, autopsy was not performed.

GENETIC ANALYSIS

In assessing the role of genetic factors in a disease one may begin by considering whether the familial distribution of the disease fits any simple mendelian pattern. If simple dominant inheritance were involved, one would expect that one parent of each patient would have the condition. Since the calcific deposits pathognomonic of chondrodystrophia calcificans congenita disappear during childhood, their absence in the parents of affected children does not rule out dominant inheritance. However, because the disease is frequently characterized by other defects, which have not been observed in the parents or more distant relatives, it seems clear that there is no simple dominant inheritance. (We do not agree with Maitland[4] that the absence or rudimentary presence of phalanges in the father of his patients indicates a "direct hereditary transmission" since the father's defect seems to have been of quite a different type from those of the children.)

Sex-linked recessive inheritance is ruled out by the fact that the disease does not occur almost exclusively in males. Of the reported cases 22 are females and 15 males — in two reports the sex is not stated (Table 1); this is not a significant deviation from a 1:1 ratio. Furthermore, the disease does not appear in maternal uncles of patients, or elsewhere in the maternal collateral ancestry.

Rare diseases showing simple recessive inheritance are characterized by the following features: the parents of affected persons are "blood relatives" more often than one would expect from the incidence of consanguinous matings in the general population,[34, 35] and the incidence of the disease in the siblings of affected persons is that expected if each sibling has 1 chance in 4 of being affected.[34] Both these features are difficult to demonstrate in data culled from the medical literature. Nevertheless, the following analysis shows that the available facts are consistent with the hypothesis that chondrodystrophia calcificans congenita is a recessively inherited disease.

Frequency of Parental Consanguinity

The estimation of the frequency of parental consanguinity from case reports in the literature is difficult because many authors do not record the presence or absence of consanguinity in the parents of their patients. Table 1 presents the family data extracted from case reports in the literature, including the family of the patients described above. It can be seen that of 33 families reviewed, information about consanguinity is available in only 12. Of these, 4 (33 per cent) show parental consanguinity. If it is assumed that in all the cases containing no statement about consanguinity there actually was none, the incidence can be estimated as 4 out of 33 families, or 12 per cent. The true

incidence of parental consanguinity in this group of families is probably somewhere between 12 per cent and 33 per cent, and, although the numbers involved are small, it is reasonably safe to assume that this is higher than the incidence of consanguinous matings in the general population (roughly 1 per cent[34]). The evidence is therefore in favor of the hypothesis that chondrodystrophia calcificans congenita shows recessive inheritance. It is interesting that Cockayne, in a discussion of Bateman's[5] paper, suggested, on the basis that 2 of the 4 patients known to him were the offspring of cousin marriages, that the disease was probably recessively inherited.

Frequency of the Disease in Siblings of Patients

The estimation from the literature of the frequency of recurrence of a disease in the siblings of affected persons is complicated by several factors. In the first place familial cases attract more attention than sporadic cases, and thus may be reported in the literature with undue frequency. Chondrodystrophia calcificans congenita is so rare that cases are likely to be reported whether they are sporadic

TABLE 1. *Familial Distribution of Chondrodystrophia Calcificans Congenita.**

AUTHOR	SIBSHIP	CONSANGUINITY IN PARENTS	REMARKS
Bateman[5]..... Case 1	F	No	Only child
Case 2	M	No	No mention of siblings
Case 3	M M	Yes	Lightwood's case; only child.
Berrey and Kimball[24]	F	Not	Only child
Bloxsom and Johnston[25]	F	?	Only child
Borovsky and Arendt[12]	M	?	No mention of siblings
Burckhardt[6]	U U F	?	Redescribed by Fancon
Conradi[3]	U U U U F	?	3 siblings died at 3, 6 & 13 mo. of unknown cause
Coughlin, Guare and Moskovitz[27]	F U† U†	Not	—
De Toni and Papio[13]	F	Yes	As cited by Swoboda[13]; no mention of siblings.
Fairbank[28]..... Case 1	F	?	No mention of siblings
Case 2	F	?	No mention of siblings
Ford, Schneider and Brandon[7]..... Case 1	U U U U M	?	2 siblings died of congenital heart disease
Case 2	U M M	?	Birth order not stated
Geyman[31]	U	?	Only child
Hässler and Schallock[29]..... Case 1	M	?	Only child
Case 2	U U U F	?	—
Haynes and Wagner[30]	U M	?	—
Hilliard[18]	F	?	No mention of siblings
Hünermann[2]	U F	?	First 2 pregnancies miscarried
Jorup[19]	F F	?	—
Kampf[20]	F	?	No mention of siblings
Lund[14]	F	?	Only child
Maitland[4]	M F F F	No	—
Putschar[21]	M M† F†	Yes†	—
Raap[22]	F M M M	Not	Concordant like-sexed twins; zygosity not stated.
Savignac[16]	M F M†	Not	—
Schönenberg and Schallock[26]	F M	?	—
Swoboda[13]	M	?	No mention of siblings; "abortive" case.
Tisdall and Erb[15]	U M	Yes	—
Vinke and Duffy[23]	M F	—	—
Wiskott[33]	U U U F	?	—
Present series	M F F	No	—

*Legend:
F = female
M = male
U = sex not stated
† Personal communication.

Underlined means affected.
Propositus is underlined twice.

or familial, so that this sort of bias may be relatively slight in the present series. Secondly, authors may fail to mention the presence of normal siblings in their case reports; this tends to give an unduly high estimate of the frequency of siblings affected. Finally, the siblings of patients may not be examined, and some with the disease may be missed, tending to give an unduly low estimate of the incidence of affected siblings.

Table 1 shows that, contrary to Fairbank's[3] statement that "there is no evidence of hereditary influence and seldom of familial influence," 6 of the 33 reported families contained more than 1 case. If the 8 families in which no mention of siblings is made are excluded, there are 6 cases of familial occurrence in 25 families — an appreciable proportion.

Haynes and Wangner[8] describe a case of chondrodystrophia calcificans congenita in a second-born infant with a first-born sibling in whom the diagnosis had been made by means of x-ray examination in the sixth intrauterine month as a case of achondroplasia fetalis; the sibling was stillborn, but no postpartum x-ray examination was made or autopsy performed. We have assumed, since no other family has been reported containing cases of achondroplasia and chondrodystrophia calcificans congenita, that the first child in the family studied by Haynes had chondrodystrophia and would have shown pathologic calcification on post-partum x-ray examination. Maitland[4] reports 2 out of 4 siblings affected. Raap[31] described a pair of male twins (there is no evidence that the twins were identical), both with the disease, which also appeared in another sibling. The first child in this family, a two-and-a-half-year-old girl, showed a few punctate densities in wrists and ankles, but we have not included her as having been affected. Vinke and Duffy[25] described 2 siblings, both of whom had the disease. In the family described by Putschar[11] another child with chondrodystrophia has been born since his report was written.[36] The present family constitutes the sixth case of familial occurrence. The family reported by Curth[21] may represent another familial occurrence. Two of 6 children had many features of the disease, but x-ray examination in infancy to demonstrate calcific stippling was not performed. They have therefore been omitted from the analysis.

TABLE 2. *Familial Distribution of Chondrodystrophia Calcificans Congenita and Theoretical Expectation for Simple Mendelian Recessive Inheritance.*[37]

No. in Family	No. of Families	Expected No. of Babies Affected	Actual No. of Babies Affected
2	6	6.85	8
3	6	7.78	8
4	3	4.38	4
5	2	3.27	2
Totals.....		22.28	22

Table 1 also demonstrates that among the 36 siblings of the propositi, or index cases, 6 were affected. (The twin of Raap's[31] propositus is assumed to have been monozygotic, and is therefore excluded from the sibling analysis.) To decide whether this proportion of familial cases fits the expectation for simple recessive inheritance, one must apply one of the statistical methods for correcting the bias arising from the method of collecting the data[37] (Table 2). Families with only 1 child are excluded from the table since they contribute no information about familial distribution. The cases reported in this paper are also omitted, for they came to our attention because of their familial occurrence. It can be seen that the observed number of affected children in families containing at least 1 affected child is 22. This corresponds closely to the theoretical expectation of 22.3. It is clear, therefore, that the familial distribution of chondrodystrophia calcificans congenita is that expected of a disease showing simple mendelian recessive inheritance.

Discussion

Although the numbers involved in the analysis presented above are relatively small and should be supplemented by future observations, they show that the familial characteristics of chondrodystrophia calcificans congenita are consistent with those expected of diseases showing simple recessive mendelian inheritance. The disease occurs in the offspring of unaffected parents, and appears in 6 of 36 siblings of affected patients, a frequency compatible with that expected if each child in the family has a 25 per cent chance of being affected. Finally, the frequency of consanguinous matings in the parents of affected persons appears higher than that in the general population, being estimated as between 12 and 33 per cent.

In the family in the case reported above, the mother had no history or signs of metabolic disease, and had normal values for serum calcium, phosphorus and alkaline phosphatase. There was no history of infections or other unusual events in any of her pregnancies. This case therefore provides no support for the possibility that a maternal, nongenetic factor caused the embryonic defects.[22] It is, in any event, difficult to imagine a hypothetical maternal factor that could affect the first and third child, but not the second, that involves 1 of every 4 children of mothers carrying the factor, and that occurs with increased frequency in mothers who marry relatives. A recessive gene pair, on the other hand, adequately accounts for the known facts.

In view of the data presented above, we believe that there is no justification for considering the disease a developmental accident, sporadic in nature.

The parents of a child with chondrodystrophia calcificans congenita should be warned that the disease may recur in later children, probably with a 25 per cent risk for each subsequent child.

Summary

Two cases of chondrodystrophia calcificans congenita occurring in one family are described. A review of the literature demonstrates that the familial distribution of this disease is compatible with the hypothesis that the disease shows simple recessive mendelian inheritance. Parents of a child with chondrodystrophia calcificans congenita may therefore be warned that any subsequent child probably has 1 chance in 4 of being affected.

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ACUTE PERICARDITIS ASSOCIATED WITH SERUM SICKNESS*

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ALTHOUGH carditis has been described as a manifestation of serum sickness in man, reports of acute pericarditis are uncommon. Davidson[1] described an increase in cardiac dullness in 72 per cent of 50 cases of serum sickness, with an average increase of 1 cm. in transverse diameter of the heart. No subjective or objective evidence of heart disease was found in any of these patients, and it was assumed that the cardiac enlargement resulted from edema of the muscular wall of the heart. Clark and Kaplan[2] reported 2 cases with endocardial and myocardial lesions, without pericardial involvement, after antipneumococcus serum. Clark[3] presented a case of poliomyelitis in which serum sickness followed the administration of horse serum; autopsy revealed cellular infiltration of the myocardium and a normal pericardium. Storey[4] reported 4 cases of serum sickness in children in association with the administration of foreign serum, either diphtheria antitoxin or tetanus antitoxin. However, in 2 of these cases there was an associated tonsillitis, raising a question of rheumatic fever as the cause. The diagnosis of carditis was based on the finding of cardiac enlargement by percussion in 3 cases and the presence of an apical systolic murmur in all 4. Fox and Messeloff[5] and Neustadt[6] described patients with serum sickness resulting from tetanus antitoxin whose electrocardiograms showed T-wave alterations during the illness; no clinical manifestations of carditis were observed. Experimental cardiac lesions of the rheumatic type produced by anaphylactic hypersensitivity with horse serum were reported by Rich and Gregory[7] and others. Focal collagen alterations, Aschoff bodies and nonspecific inflammatory lesions simulating human rheumatic carditis were noted in the animals. Rich and Gregory[8] and More and Kobernick[9] described pericardial inflammatory changes in rabbits induced by hypersensitivity to horse serum.

Rosenhaupt,[10] in 1905, reported a case of serum sickness resulting from diphtheria antitoxin. During the course of this illness the patient became cyanotic and dyspneic. Physical examination revealed cardiac enlargement, poor heart tones and no pericardial friction rub. This was diagnosed clinically as pericardial effusion. Recovery occurred in ten days. Wadsworth and Brown[11] described a case of carditis occurring with serum sickness after tetanus antitoxin. During an eighteen-week period of observation a presystolic gallop, friction rub, apical diastolic murmur and electrocardiographic evidence of hypertrophy of the right ventricle were described. Although this case is regarded as one of carditis complicating serum reaction, one wonders about the alternative diagnosis of rheumatic carditis. McKinlay[12] reported a case in which carditis, pericarditis and pleurisy followed administration of tetanus antitoxin. During the manifestations of the serum sickness the patient complained of precordial pain and dyspnea. No cardiac abnormalities were noted at that time. Approximately a month after the subsidence of the usual objective signs of serum sickness, when the patient still complained of precordial pain, clinical and x-ray examination revealed cardiac enlargement, an apical systolic murmur, a loud pericardial friction rub, a separate left pleural friction rub and later a left pleural effusion. Serial electrocardiograms showed inversion of the T waves in Leads 1, 2 and 4. Complete recovery, with reversion of the chest roentgenograms and electrocardiograms to normal, occurred within a month. Willius[13] is credited with reporting a case of pericarditis resulting from serum sickness,[14] which followed administration of diphtheria antitoxin for an acute pharyngitis (diphtheria suspected). Two and a half weeks after the subsidence of the manifestations of the serum sickness, a typical acute pericarditis developed, followed by recovery within a few days.

CASE REPORTS

CASE 1. One of us (M.J.G.) had the opportunity, in 1937, of observing a 15-year-old boy in whom serum sickness followed the administration of tetanus antitoxin. This was manifested by fever, generalized urticaria and painful swelling of many peripheral joints. Simultaneously, the patient complained of severe precordial pain.

Physical examination revealed an increased area of cardiac dullness and a loud pericardial friction rub. Unfortunately, the hospital record cannot be found for a description of the laboratory data. Complete recovery occurred within 2 weeks.

CASE 2. A 35-year-old Negro laborer was admitted to the hospital on June 23, 1953, for an acute illness that had begun at noon on the previous day and was characterized by swelling of the lips, eyelids and cheeks. The patient stated that he had noted "hives" over the whole body shortly after the swelling of the face occurred. This was accompanied by malaise, sweats and feverishness. On the morning of admission he observed pain, swelling and tenderness in the knees, ankles, wrists, hands, shoulders and right hip. The involved joints were so tender that even the movement of the bed covers over them caused excruciating pain. On questioning he stated that he also had pain over the left anterior aspect of the chest centering about the 7th rib in the parasternal line on deep breathing or coughing. This chest pain was not noticeable on swallowing, yawning or change of position.

There was no recent history of sore throat, urethral discharge or diarrhea and no past history of tuberculosis. He stated that on June 15 he had received injections of tetanus antitoxin and penicillin as a prophylactic treatment for a human bite received

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on June 14. This treatment was verified from the Emergency Room record of the Alameda County Hospital, which revealed that a skin test done before the administration of tetanus antitoxin demonstrated no immediate sensitivity reaction. The patient stated that he had received tetanus immunizations several times during Navy service but that he had no recollection of tetanus antitoxin injections except for the recent one given. He denied having any serious illnesses for which he had

Urinalysis demonstrated a specific gravity of 1.018, a negative test for albumin and acetone and a ++ test for sugar; the sediment contained 2 white blood cells per high-power field. Examination of the blood showed a red-cell count of 5,300,000, with a hemoglobin of 16.4 gm. per 100 cc., and a white-cell count of 8500, with 60 per cent neutrophils, 24 per cent lymphocytes and 1 per cent eosinophils. The blood Kahn test was negative. The blood urea nitrogen was 13 mg. per 100 cc. Heterophil-anti-

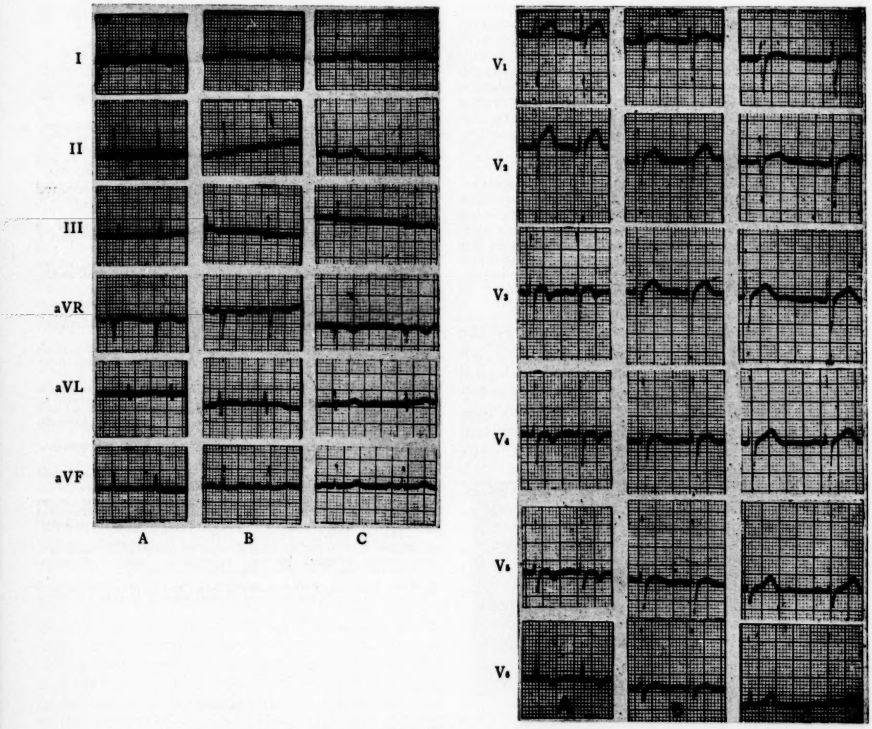

FIGURE 1. *Serial Electrocardiograms, Showing Tracings at 3 p.m. on the Day of Admission* (A), *Twenty Hours after Administration of Cortisone* (B) *and Three Days after Admission* (C).

received serum. Although he had received penicillin on several occasions he denied any reactions to this drug.

Physical examination showed a well nourished man, 6 feet, 1½ inches tall and weighing 190 pounds, who appeared acutely ill. The face was markedly swollen, mainly in the periorbital and perioral areas. The pharyngeal cavities revealed no inflammatory changes. Bilateral, nontender, enlarged posterior cervical lymph nodes were present. Examination of the heart disclosed a definite, loud pericardial rub, which changed in intensity through the respiratory cycle but persisted even when the breath was held. The wrists, hands, knees and ankles were swollen, painful and tender and warmer than other unaffected portions of the body. There were no specific skin lesions.

The temperature was 101°F., the pulse 88 and regular, and the blood pressure 130/90.

body agglutination was positive in a titer of 1:28 on admission and in a titer of 1:7 3 days later. A roentgenogram of the chest was normal. An electrocardiogram taken on admission revealed inverted T waves in leads aVL, aVF and V_3 to V_6 — findings regarded as consistent with pericarditis (Fig. 1).

The patient was acutely ill on admission, resisting vigorously any movement of his body. He was given sedatives and analgesics as needed, and after his initial work-up an initial dose of 250 mg. of cortisone was administered by mouth. Within the first 20 hours after a total dose of 300 mg. of cortisone there was moderate improvement, with less swelling of the face, wrists and hands, but swelling of the knees persisted. The pericardial rub was absent 20 hours after admission although pain in the left anterior aspect of the chest on deep breathing or coughing persisted. The temperature became normal within 24 hours. The

electrocardiogram demonstrated upright but low T waves in comparison with the initial tracing (Fig. 1*B*). Cortisone, 50 mg. twice daily, was continued until June 29, although the patient was symptom free and ambulatory on June 26, when serial electrocardiograms revealed changes reverting to normal. Interestingly enough, on June 30, an electrocardiogram taken 20 hours after discontinuance of cortisone showed the T waves again to be of low amplitude to inverted (however, an electrocardiogram taken on July 2 revealed upright T waves of normal amplitude). On June 30 300,000 units of procaine penicillin was given as a provocative test but did not evoke any reaction. Five follow-up chest roentgenograms showed no pulmonary or cardiac lesions. A glucose tolerance test performed on July 1, to check the admission ++ test for sugar before cortisone administration, disclosed the following values: fasting, 95 mg., at ½ hour, 145 mg., at 1 hour, 110 mg., at 2 hours, 105 mg., and at 3 hours 80 mg. per 100 cc. The urine gave a + test for sugar at ½ hour, 1 hour and 2 hours. A repeat glucose tolerance test on July 10 had the following results: fasting, 80 mg., at ½ hour, 100 mg., at 1 hour, 65 mg., at 2 hours, 75 mg., and at 3 hours, 80 mg. per 100 cc. All tests for sugar in the urine were negative. It was thought that both the ++ test for sugar on admission and the first glucose tolerance curve probably represented a low renal threshold for glucose during the serum sickness.

On a follow-up visit on July 9 the patient was symptom free and had no abnormal physical findings. An electrocardiogram and a roentgenogram of the chest were within normal limits.

Discussion

It is not the purpose of this paper to discuss the relation between serum sickness and the other collagen diseases. On clinical grounds it seems logical that since joint involvement is a common manifestation of serum sickness, other serous surfaces, such as the pericardium, can likewise be involved. The data presented above confirm this. It is quite possible that pericarditis or myocarditis or both occur more commonly than they are clinically recognized. A pericardial friction rub is often transitory and faint. Electrocardiograms, naturally, are not often taken in such a self-limited condition, especially when there is no definite clinical evidence of heart disease. It is hoped that this report will stimulate interest to look for further cases by careful physical examination of the heart and by electrocardiographic study whenever practical.

Summary

Two cases in which acute pericarditis occurred in association with serum sickness resulting from tetanus antitoxin are reported. The literature on the subject is reviewed.

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"WHEAT-FREE" DIET IN THE TREATMENT OF SPRUE*

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THROUGHOUT the years diet has played an important part in the treatment of the steatorrhea of sprue and of celiac disease. Although the relation between these two diseases has never been established clearly, they are clinically similar in many respects — so much so that some investigators consider them to be the same disease in different age groups.[1]

Because of the steatorrhea a low-fat diet has been advocated in both disorders. In fact, until recently, the accepted dietary treatment of sprue was a high-protein, high-carbohydrate, high-vitamin, low-fat diet.[2] In celiac disease, on the contrary, other regimens have been suggested. Haas,[3] in 1924, recommended a "banana" diet and reported favorable results. Fanconi,[4] in 1928, advocated a "vegetable-fruit" diet and likewise noted clinical improvement. Andersen,[5] in 1947, and Sheldon,[6] in 1949, reported that a "starch-free" diet had a favorable clinical effect and lowered the fat content of the stools in celiac disease. More recently a "low-starch" diet has been advocated in the treatment of sprue.[7]

Interest in the dietary management of celiac disease was revived recently by the important observation of Dicke[8] and by the carefully conducted studies of Weijers and van de Kamer.[9] These investigators noted that patients with celiac disease improved when wheat and rye flour were excluded from the diet, and showed conclusively that a clinical and biochemical remission followed institution of a "wheat-free" diet. Further investigation incriminated the gluten fraction of wheat and rye as the responsible factor.

The close similarity between celiac disease and sprue led us to believe that a "wheat-free" diet might be beneficial in the management of sprue. Because of the astonishing remission after the institution of this diet in a patient with sprue, a detailed case report was considered justified.

CASE REPORT

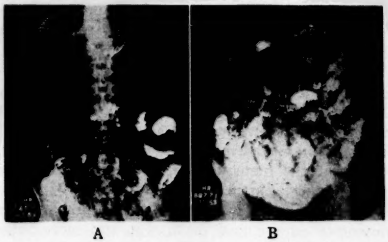
D. M. (D.H.-58771), a 39-year-old housewife, was admitted to the hospital on February 22, 1953, with a chief complaint of diarrhea and weight loss over a period of 12 years.

The illness had begun at the age of 27 after a trip to South America, at which time she noted the sudden onset of diarrhea, nausea, vomiting and abdominal pain. The stools were loose, putty colored, bulky and greasy. An oral glucose tolerance test at that time revealed a fasting blood sugar of 120 mg. per 100 cc., with a flat absorption curve. The fat content of the stool was elevated, and free hydrochloric acid was present in the gastric secretions. A diagnosis of sprue was made, and a low-fat, low-protein, high-carbohydrate diet, supplemented by vitamins and liver extract intramuscularly, was prescribed. The patient continued to lose weight and had intermittent spells of diarrhea, with as many as 28 stools a day. Throughout the following 12 years, she had numerous recurrences, and her weight continued to decline, varying between 95 and 100 pounds. During remissions she had 2 or 3 loosely formed stools daily. Anemia was not observed at any time throughout the illness. In recent years she had followed her diet carefully, supplemented by vitamin B_{12}, folic acid, liver extract and calcium. Two months before admission she had a severe relapse, which did not respond to intensive therapy.

Physical examination revealed a poorly nourished woman weighing 89 pounds. The blood pressure was 86/56. The tongue was normal, and the abdomen was distended and tympanitic; there was slight edema of the lower extremities.

Examination of the blood disclosed a red-cell count of 5,200,000, with a hemoglobin of 13.2 gm. per 100 cc., and a normal white-cell and differential count. Urinalysis was negative. A stool sample was soft, foamy and putty colored, with a marked increase in fat as demonstrated by Sudan III stain. The total protein was 6.1 gm., with an albumin of 3.0 and a globulin of 3.1 gm. per 100 cc.; the calcium was 5.5 mg., and the phosphorus 2.5 mg. per 100 cc. A glucose tolerance test was 80 mg. per 100 cc. fasting, 117 mg. at ½ hour, 107 mg. at 1 hour and 93 mg. at 2 hours. A vitamin A tolerance test was 21 microgm. per 100 cc. fasting, 21 microgm. at 3 hours and 21 microgm. at 5 hours.

X-ray studies showed the esophagus, stomach and duodenum to be normal. The jejunal pattern was strikingly abnormal, with thickened folds, fragmentation, segmentation and flocculation of the barium. The lumen varied greatly in diameter and the classic moulage sign was present. The ileum revealed the same changes.



A B

FIGURE 1. *X-Ray Studies.*

Before treatment (A) *the small-bowel study shows flocculation, segmentation, dilatation and the characteristic moulage sign. After treatment* (B) *the small bowel appears entirely normal. (Note the absence of flocculation, segmentation, dilatation and moulage sign.) The normal appearance after treatment persisted throughout the entire six-hour study.*

On February 27 the patient was given a "wheat-free" diet with no medication except calcium. Within a few days she began to improve, and 2 weeks later reported that she felt better than she had in any previous remission. Her bowel movements decreased to 2 formed stools a day, and she had gained 4 pounds in weight at the time of discharge 2 weeks after starting the "wheat-free" diet. There was no material change in the blood chemical constituents, absorption curves or x-ray films at that time.

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She was re-admitted to the hospital on June 8, approximately 3 months after starting the "wheat-free" diet, and reported that she felt better than she had at any time since her illness began 12 years previously. She now weighed 132 pounds — a gain of 43 pounds. Her diarrhea had ceased, and the stools were grossly normal, 1 or 2 solid, formed stools a day. An episode of diarrhea, nausea and vomiting lasting 24 hours had followed ingestion of wheat.

Physical examination revealed a slightly obese woman who appeared to be in excellent health. No abnormalities were noted. The blood pressure was 105/60.

Examination of the blood disclosed a red-cell count of 4,480,000, with a hemoglobin of 12 mg. per 100 cc., and a normal white-cell and differential count. Urinalysis was negative. Sudan III stain on a stool demonstrated a normal amount of fat. The total protein was 7.3 gm., the albumin 4.3 gm., the globulin 3.0 gm., and the calcium 9.2 mg. per 100 cc. A glucose tolerance test gave the following results: fasting, 120 mg., at 30 minutes, 135 mg., at 1 hour, 145 mg., at 2 hours, 144 mg., and at 3 hours, 119 mg. per 100 cc. The vitamin A tolerance was 46 microgm. per 100 cc. fasting, 59 microgm. at 3 hours and 66 microgm. at 5 hours.

Barium studies showed a normal esophagus, stomach and duodenum. In striking contrast to the previous study, however, the jejunal and ileal patterns were entirely normal (Fig. 1).

The striking clinical features of this patient's response to a "wheat-free" diet were the marked subjective improvement, the rapid restoration of a sense of well-being, the cessation of diarrhea and a 43-pound weight gain. Biochemically, the greatest changes were noted in total protein and serum calcium, both of which reverted to normal. There was improvement in the absorption of both glucose and vitamin A, although neither returned to normal levels. Equally striking was the complete reversion to normal of the radiologic appearance of the small bowel.

Discussion

It is unwise to draw conclusions concerning the value of a drug or procedure in the treatment of a chronic disease from observations on a single patient. This is especially true when the disease is characterized by unpredictable remissions and exacerbations. Nevertheless, the rapid and dramatic improvement in this patient after the institution of a "wheat-free" diet without supplemental therapy strongly suggests that the remission was induced rather than spontaneous. Furthermore, the patient insisted that this particular remission was unlike any previously experienced in that it was more complete. A similar response in a patient with sprue reported by McIver[10] lends additional support to the conclusions that the "wheat-free" diet was the responsible factor.

The change in the radiologic appearance of the small bowel after institution of the "wheat-free" diet was astonishing. In our experience and in that of others, the small-bowel pattern rarely returns to normal during remissions, whether induced or spontaneous.[11-13] In this patient, on the contrary, the pattern reverted entirely to normal within three months of the beginning of treatment. (The radiologic study of the small bowel both before and after treatment was performed with a barium sulfate water mixture.)

The tendency of the blood chemical constituents to revert to normal is characteristic of remission. In this case the total protein, albumin-globulin ratio and serum calcium all became normal. The vitamin A and glucose tolerance curves indicated improvement in absorption although they did not revert entirely to normal levels.

It should be emphasized that this patient had been treated intensively with folic acid, liver extract and vitamin B_{12} over a period of many years, and in spite of this therapy was in severe relapse at the time of the institution of the "wheat-free" diet. It should be emphasized further that the "wheat-free" diet was the only treatment administered except calcium.

The improvement reported in the past in the dietary treatment of sprue and of celiac disease may well have been due to the absence of wheat in these diets, since a factor in common in the "banana" diet, the "vegetable-fruit" diet and the "starch-free" diet is the elimination or marked curtailment of wheat.

Although the observations in this case suggest that a "wheat-free" diet induces a clinical remission in sprue, it is impossible to predict that the remission will be sustained without supplemental therapy, especially with hematopoietic agents. It would be interesting to determine whether the "wheat-free" diet has a specific effect in sprue, or if it would be equally beneficial in steatorrhea from other causes.

Conclusion

Preliminary observations indicate that a "wheat-free" diet may induce a clinical, biochemical and radiologic remission in patients with sprue.

Two additional patients with the "sprue syndrome" have been treated with the "wheat-free" diet. Each experienced the same striking clinical remission described in the case reported above. Radiologic study of the small bowel was performed in only 1 of these patients before and after the institution of the diet, and again the markedly abnormal pattern reverted entirely to normal. Further study of the patients is in progress.

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MEDICAL PROGRESS

A DECADE OF PROGRESS IN THE Rh BLOOD-GROUP SYSTEM*

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THE importance of the Rh factor is now well appreciated by both the physician and the layman. Understanding of the basic concept of isoimmunization by blood transfusion or by pregnancy requires only the knowledge that blood may be classified as "Rh positive" and "Rh negative." This was illustrated by Diamond's[1] review in 1945, which described all the clinical manifestations associated with intragroup incompatibility of mother and fetus, or donor and recipient. After eight years it is scarcely possible to add anything to the essential principles on which understanding of the pathology of these conditions is based. But a great deal of detailed information regarding the genetics and immunology of the Rh factor has become available since that time, culminating in the recent discovery of a "new" Rh antigen.[2,3] The Rh family is now large, at least eleven separate antigenic members being recognizable, but fortunately the Fisher–Race system provides a rational method of integrating knowledge of these blood factors.

Fisher,[4] in 1944, postulated that the inheritance of the Rh antigens was determined by three closely linked genes, each capable of existing in an allelic (or alternate) form; at that time it was thought that only two alleles of each of the three genes existed. The genes occupying each of the three available positions (loci) on the chromosome were named C, D and E, and their alleles or alternates were identified by the lower-case letters c, d and e. Each of the genes present on the Rh chromosome conferred upon the red cell a specific antigenic property, the antigen bearing the same name as the gene that had determined it. In other words, there was said to be a one-to-one correspondence between genes and antigens. For example, a person, one of whose Rh chromosomes bore the genes CDe, would have in his red cells the antigens C, D and e. The antiserums capable of identifying the separate Rh antigens were, in logical fashion, named anti-C, anti-D and so forth. It is important to emphasize at this point that the commonly used terms "Rh positive" and "Rh negative" refer to the presence or absence of the D antigen only because it is clinically the most important factor. The anti-Rh serum anti-D differentiates bloods into those that contain the D antigen and those that do not.

When the Fisher theory of linked allelomorphic genes was first advanced only four distinct anti-Rh serums were known. These were anti-C, anti-D, anti-E and anti-c. Since Fisher's theory called for the existence of a red-cell antigen e determined by the gene e (which was allelomorphic or alternative to E), it was necessary to suppose the existence of an antiserum anti-e although this antibody had not yet been discovered. Table 1 shows the chromosomes that had been positively identified on the basis of Rh antigens in the red cells of various persons up to 1944.

TABLE 1. *Known and Predicted Reactions of the Rh System in 1944.**

ANTISERUM	CHROMOSOMES AND ANTIGEN COMBINATIONS							
	cDe	cde	cDE	CDe	Cde	cdE	CDE	CdE
Anti-C	0	0	0	+	+	0	(+)	(+)
Anti-D	+	0	+	+	0	0	(+)	(0)
Anti-E	0	0	+	0	0	+	(+)	(+)
Anti-c	+	+	+	0	0	+	(0)	(0)
(Anti-d)	(0)	(+)	(0)	(0)	(+)	(+)	(0)	(+)
(Anti-e)	(+)	(+)	(0)	(+)	(+)	(0)	(0)	(0)

*The reactions to be expected between the various separate anti-Rh serums and the cell antigens conferred by the possible gene combinations on *single* chromosomes. A positive reaction is indicated by the symbol +; 0 denotes no reaction. Symbols in parentheses indicate that that reaction was predicted by the theory but had not been observed at the time of publication (1944).

Reading across the first line of the table demonstrates that the anti-Rh serum, anti-C, will give a positive reaction with blood from persons either or both of whose chromosomes carry the gene C. The second line gives the reactions of anti-D with bloods from persons carrying the D gene (so-called "Rh-positive" persons). The final line of the table constitutes a set of reactions with the antibody, anti-e. The placing of the symbols of this line and other lines in parentheses indicates that these reactions had not been observed when the "linked-gene" theory was originally put forward. Through the concept of linked genes the potentialities of the Rh system were for the first time made clear: serologists and blood-group workers throughout the world were given a theory that made verifiable predictions. The value of the theory can best be appreciated if one realizes that twenty-four new reactions were forecast involving the prediction of two new antiserums and two new chromosomes.

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This is in contrast to the "Rh-Hr" system of genetics and nomenclature, which lacks the power of logical extension.

The confirmation of the reactions of the CDE chromosome by Murray, Race and Taylor[5] came in the same year that Fisher's theory was advanced, and in the following year Mourant[6] presented evidence proving the existence of anti-e. It was necessary, however, to wait three years before the rare chromosome CdE was found by Van den Bosch[7] in 1948, and, also in this year, the predictions of the original linked-gene hypothesis were completely fulfilled by the discovery of the antibody anti-d by Hill and Haberman.[8]

It is now necessary briefly to consider an important implication of the linked-gene theory. Among plants, insects and various mammals many inherited factors are known to be transmitted by linked genes. One of the characteristic features of linked-gene transmission is the possibility of a change in place of one or more of the genes of one chromosome with genes from the corresponding loci on the opposite chromosome. This exchange takes place when the chromosomes are being segregated before

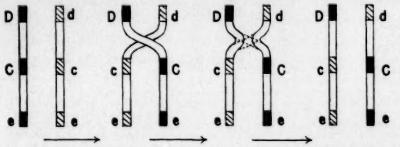

FIGURE 1. *Illustration of "Crossing over" at the Rh Chromosone. The person of genotype CDe/cde produces two gametes of type cDe and CdE respectively. (See text for explanation of the gene order.)*

the production of the gamete, — for example, in the human being, at the stage of reduction division that ends in the production of the spermatozoon or ovum, — the phenomenon being known as "crossing over." An organism developing from this altered gamete will show characteristics quite different from those of its siblings since it possesses a new gene combination as a result of the "crossover" that occurred when the gamete was formed. The Rh antigens are thought to be determined by linked genes, and so the possibility of alteration of the Rh genotype by crossing over between Rh chromosomes is a real one. Figure 1 shows schematically how crossing over between two common types of Rh chromosomes (CDe and cde) may result in the production of two uncommon chromosomes, Cde and cDe.

It will be seen from the figure (reading from left to right) that the two chromosomes come into contact between the C and D loci, but instead of separating into their original gene combinations the lower part of one chromosome becomes fused to the upper part of its fellow, and vice versa. Two "new" chromosomes are therefore produced. Fisher postulated that the relatively rare chromosomes, such as Cde, cdE and CDE, arose in this way by crossing over between pairs of the three common chromosomes CDe, cDE and cde. In the figure the gene order DCE is shown, and this order fits in best with the observed frequencies of gene combinations resulting from cross overs, but custom and common usage require that the alphabetical order be retained in the text. No example of crossing over in the Rh complex has yet been observed. This is not surprising since it must be an event of some rarity, but only 1 authenticated case of the phenomenon is needed to provide unequivocal proof of Fisher's theory.

The usefulness of the concept of triple-linked genes is perhaps most appreciated when "unusual" antigens associated with the Rh system are dealt with. In 1946 Callender and Race[9] found an antibody that identified a rare Rh antigen determined by a gene allelomorphic (that is, an alternate) to C and c. They named the antigen C^w. In terms of Fisher's theory, identification of the antigen presented no special difficulty but, in Race's[10] own words, "If Fisher had not discovered the allelomorphism of C and c and of D and d and of E and e, C^w would have presented a problem that we at any rate could not have solved." Two other alleles at the C locus have since been discovered.[11] These alleles, which are of great rarity, were named C^u and c^v.

An atypical Rh antigen of considerable clinical importance was described by Stratton[12] in 1946. It was shown to be determined by a gene allelomorphic to D, and Stratton named both gene and antigen D^u. The properties of this antigen may be summarized by the statement that blood possessing it gives weaker reactions with anti-D serum than "ordinary" D-positive blood, and its detection frequently requires the indirect Coombs test. However, though it gives weaker reactions in the test tube, blood cells containing D^u are capable of inducing the formation of anti-D in Rh-negative (cde/cde) persons, and hemolytic reactions occur if D^u blood is transfused into a person previously immunized against the D antigen. It is not possible completely to avoid these hazards by ordinary Rh typing procedures since many D^u bloods type as Rh negative unless special technics (indirect Coombs test) are used. The frequency with which the antigen D^u occurs in a population will obviously determine the clinical importance of the D^u factor in blood-transfusion practice. D^u is found quite rarely (about 1.5 per cent) in persons of European descent and then almost invariably in association with C or E, the usual genotypes of Caucasian bloods containing D^u being CD^ue/cde or cD^uE/cde. In the American Negro, however, D^u is of considerably higher frequency, being found in about 5 per cent. Furthermore, the usual type of Rh chromosome carrying the D^u gene in these people is cD^ue. The

problem posed by D^u is obviously greatest in the parts of this country where the Negro population is largest. The antigenicity of D^u or its ability to provoke an immune response when transfused into susceptible (D-negative) recipients is not exactly known. However, several examples of transfusion reaction to D^u blood have been reported, as have cases of erythroblastosis fetalis. It must therefore be assumed that D^u is sufficiently antigenic to warrant as much care in its detection as is applied to the ordinary differentiation of blood into D positive and D negative. It is most important that *every* blood bank take account of the question of D^u and never permit D^u blood donors to masquerade as true Rh-negative donors.

Although the antigenicity of D^u has not yet been properly defined there is complete agreement among all workers that "ordinary" D is a very potent antigen. Several investigators[13-15] have shown that injection of D-positive blood into D-negative persons brings about the formation of specific antibodies in more than half of such recipients.

To complete the tale of allelic genes in the Rh complex, an example of a variant of the E antigen known as E^u was described in 1950 by Ceppellini.[16] This antigen was determined by a gene E^u allelomorphic to E and e.

There is no theoretical reason why there should be a limit to the number of allelomorphic genes at a given locus, but it is not likely that any new alleles that may be discovered in the future will be common or clinically important. With the exception of D^u the less common alleles, such as C^w, c^v and E^u, are of interest mainly because of their rarity.

Great interest was aroused in 1951 by the report by Race, Sanger and Selwyn[17] of what appeared to be a chromosomal deletion, or loss of genes, at the Rh complex. The person described had an Rh genotype that could only be written $-D-/-D-$. In other words the subject's blood completely lacked the antigens C or c and E or e, and as far as could be ascertained these missing antigens were not represented by allelomorphically determined variants such as C^w and E^u. The discovery of a blood sample of this unusual type was considered by the authors to be strong evidence of the linked-gene hypothesis. The gene order DCE would fit in well with a deletion or loss of the "lower part" of the chromosome carrying the C and E loci. A similar phenomenon has been described by Wiener,[18] his patient being a Negro who apparently lacked both the antigens E and e. As the originator and strongest proponent of the multiple allele hypothesis of the inheritance of the Rh system, Wiener regarded the unusual blood reactions of his case as "readily explained" if one assumes that it is due to the influence of a rare gene, which he named R^{o_u}. Adherents of Fisher's theory consider the reactions to have been due to the simple deletion or loss of the Ee locus.

It might well be thought that the further development of knowledge of the Rh antigens would resolve itself into a filling in of detail. It was surprising, therefore, when an agglutinin was recently found in the serum of a man who had received numerous transfusions that caused reactions suggesting the existence of a "new" agglutinogen in red cells belonging to certain Rh types. Rosenfield et al.,[2] and Sanger et al.[3] who first described the reactions of the agglutinin, called it anti-f, and the agglutinogen for which this antibody was specific was called f. Jones and his associates[19] were able to show that the agglutinin anti-f was, in fact, a fairly common antibody but that its presence in a serum was usually obscured by other Rh antibodies.

General Properties of the f Antigen

Sufficient data have now been accumulated to enable a reasonably firm definition of the f antigen to be made. It seems that there is a remarkably close association between the gene combination ce and the presence of the f antigen in the red cells. Cells that possess the factor are those derived from persons who have one or both chromosomes of Type cde, cDe or cD^ue (where c and e are on the same chromosome), whereas a person whose Rh chromosomes are of any other type (with c and e not on the same chromosome) lacks the factor. It is important to appreciate that if the genes c and e are present but on *opposite* chromosomes (as in the genotype CDe/cDE) the f antigen is absent from the cells.

Although the association between the genes c and e and the antigen f is close it does not seem to be invariable. During a recent survey of the frequency of the antigen among selected bloods of known type, 34 bloods of Type CDe/cde were examined for the presence of f, and 3 were found to lack it. The finding of "exceptions" to the rule raises certain points in connection with the genetics of f that are dealt with below in a later section.

Properties of the anti-f Antibody (Comparison of anti-f and anti-d)

Definition of the anti-f antibody depends on two criteria: the person who has made the antibody should himself be f negative; and the antibody should react in the expected fashion with certain critical bloods.

Regarding the first criterion, all examples of anti-f found up to the present have been produced by persons of the genotypes CDe/cDE, CDe/CDe and cDE/cDE (Table 2). But there is no theoretical reason why persons with the rarer genotypes such as CDe/cdE and CDe/Cde (or any other f-negative person) may not produce anti-f if stimulated with the appropriate cells.

At first sight the anti-f antibody may appear to resemble anti-d so far as it will agglutinate all "Rh-negative" (cde/cde) and "heterozygous Rh-

positive" (for example, CDe/cde and cDE/cde) cells and will fail to agglutinate "homozygous Rh-positive" cells (such as CDe/CDe, cDE/cDE and CDe/cDE). Since the "zygosity" of most cells is determined by an intelligent guess based on results obtained with the five usual anti-Rh typing serums the illusion of the resemblance of anti-d to anti-f will be maintained unless the true genotypes of the cells used in the test are obtained by family study. In this laboratory two types of family have been used for this purpose, examples of each being given in Tables 3 and 4.

TABLE 2. *Genotypes of Persons Producing anti-f.*

GENOTYPE OF DONOR	REMARKS
CDe/cDE*	Anti-N, anti-S and anti-K present in addition to anti-f
CDe/CDe	Associated with anti-c
cDE/cDE†	Associated with anti-e

*The original donor described by Rosenfield et al.[3]
†Donor described by Jones et al.[19]

The results shown in Table 3 clearly indicate that the red cells of the first child must contain the antigen d. At the same time the child does not possess the gene combination ce on either of his Rh chromosomes, and therefore his cells will lack the f antigen. These cells would be expected to give a positive reaction with anti-d and a negative reaction with anti-f. This result with anti-f was confirmed in fact.

The results shown in Table 4 provide a corollary. In this family the critical blood is that of the father, whose two chromosomes CDe and cDe each show up clearly in his children: his cells lack the d antigen and would not be agglutinated by an anti-d serum, but since one of his chromosomes has the ce gene combination a positive result with anti-f would be expected and was indeed found.

These families afford only two examples of critical bloods with which anti-f will react differently from the hypothetical anti-d. Table 5 gives a more complete list of alternative critical genotypes, but most of these would be more difficult to find and to identify than the examples cited here.

Anti-f in Association with Other anti-Rh Antibodies

Consideration of the genotypes of persons who develop anti-c or anti-e leads immediately to the conclusion that these persons are also potentially capable of producing anti-f since they invariably lack the gene combination ce on both Rh chromosomes, their cells thus being f negative. Furthermore, immunization is usually brought about in such persons by their exposure to the antigenic stimulus of f-positive cells (that is, cells with a genotype involving at least one cde chromosome). A typical example is to be found in the following case report:

The blood of Mrs. Ke was tested during the course of her 2d pregnancy and found to be Type CDe/CDe. Her serum contained an antibody of mixed saline-active and albumin-active type, with a titer of 1:32 and anti-c specificity. The blood type of Mrs. Ke's husband was cde/cde. At full term Mrs. Ke gave birth to a severely erythroblastotic fetus with a strongly positive direct Coombs test, the blood type of the fetus being CDe/cde. A post-partum specimen of serum from the mother was tested for the presence of anti-f by absorption with several volumes of cDE/cDE cells, the object of this procedure being to remove the anti-c without affecting any anti-f that might be present. After this absorption the serum was found no longer to react with cDE/cDE or CDe/cDE cells by any of the usual technics, proving that all the anti-c had been removed, but it still contained a saline-active antibody that strongly agglutinated all Rh-negative (cde/cde) cells and successfully met the criteria for the identification of anti-f.

The same technic was applied to two different samples of pooled anti-c serum that were used in

TABLE 3. *Genotypes of the Members of a Family Supplying One of the Critical Bloods That Permit a Distinction between anti-f and the Hypothetical anti-d.**

MEMBER OF FAMILY	OBSERVED REACTION ANTI-C	ANTI-D	ANTI-E	ANTI-c	ANTI-e	GENOTYPE	OBSERVED REACTION ANTI-f	EXPECTED REACTION ANTI-d
Father	+	+	0	0	+	CDe/CDe	0	0
Mother	0	0	+	+	+	cde/cdE	+	+
1st child	+	+	0	+	+	CDe/cdE	0	+
2d child	+	+	0	+	+	CDe/cde	+	+

*Reactions of the critical blood shown in heavy type.

TABLE 4. *Second Example of a Family That Contributes a Critical Blood Permitting Differentiation of anti-f from anti-d.*

MEMBER OF FAMILY	OBSERVED REACTION ANTI-C	ANTI-D	ANTI-E	ANTI-c	ANTI-e	GENOTYPE	OBSERVED REACTION ANTI-f	EXPECTED REACTION ANTI-d
Father	+	+	0	+	+	CDe/cDe	+	0
Mother	0	0	0	+	+	cde/cde	+	+
1st child	+	+	0	+	+	CDe/cde	+	+
2d child	0	+	0	+	+	cDe/cde	+	+

this laboratory as typing reagents — that is, the serums were thoroughly absorbed with cells selected so that they contained the c antigen and lacked the f antigen. In each of the samples a residual saline-active antibody, which was identified as anti-f, remained after absorption of the anti-c.

At the same time two different samples of anti-e were tested for the presence of anti-f by absorption with CDe/CDe cells. One of these serums was a commercial typing reagent; the other was an anti-serum from a volunteer of type cDE/cDE who had received many injections of Rh-negative cells. Both serums were shown to contain anti-f in addition to anti-e.

Two further anti-c serums were available that differed from the foregoing samples by having been produced in response to immunization with blood of a type expected to be f negative. Both were from women of Type CDe/CDe who had become immunized by pregnancy. The blood types of their husbands were CDe/cDE and cDE/cDE. These serums were tested for the presence of anti-f by removal of the anti-c by absorption, but in neither case was anti-f demonstrable after absorption. The serums, however, were not "pure" antibodies since both gave a positive reaction with blood of Type CDe/CdE, demonstrating that the anti-c was accompanied by anti-E in each case. It should be noted that the absorption experiment described in connection with these serums provides only negative evidence for the absence of anti-f.

The conclusion to be drawn from these findings is that a proportion (as yet unknown) of all anti-c and anti-e typing reagents must be expected also to contain anti-f. The significance of this state of affairs is discussed below.

Further Properties of anti-f

The relatively few examples of anti-f isolated in this laboratory by the absorption technic have all proved to be saline-active antibodies. Furthermore, the crude serums from which these specific antibodies were obtained shared the property of readily agglutinating saline suspensions of f-positive cells while requiring the addition of albumin before they would agglutinate cells that were c or e positive but f negative. The two samples of anti-c serum that were thought not to contain anti-f were active only in the presence of albumin. This difference in behavior might be used as a rough guide tentatively to determine the presence or absence of anti-f in a same time possessed the f antigen. In spite of exhaustive searching such a blood has not yet been found. At present, therefore, only negative evidence of the type cited above is available. Some success has been obtained in this laboratory in the preparation of "pure" anti-e by eluting the antibody from the stroma of CDe/CDe cells previously coated with one of the available anti-e + f serums, but this study has been placed in abeyance pending the discovery of a suitable cell for the definitive testing of the eluates.

serum. For example, an anti-c serum that agglutinated Rh-negative cells in saline solution but required the addition of albumin to agglutinate cDE/cDE cells might be thought to contain anti-f.

Although it is a simple matter to prove that an anti-c or anti-e serum also contains anti-f at present it seems impossible to prove beyond doubt that such a serum does *not* contain anti-f. To disprove the presence of anti-f in a conclusive manner it would be necessary to test the serum with a blood that lacked the c antigen (or the e antigen) but at the

TABLE 5. *Genotypes of Bloods That Permit a Distinction between anti-f and anti-d.*

Genotypes positive with anti-f but negative with anti-d*	cDe/cDe	cDe/cDE	cDe/CDe	cDe/CDE
Genotypes positive with anti-d but negative with anti-f	CDe/CDe CDe/cdE	Cde/Cde CDe/CdE	Cde/cDE cDE/cdE	Cde/cdE cdE/cdE

*Note that the list of genotypes of cells that are expected to be positive with anti-d but negative with anti-f is not complete, exceedingly rare types having been omitted.

Genetics of f

It is necessary to consider the ways in which the sudden emergence of the new antigen may be most plausibly fitted into the existing framework of genetic theory regarding the inheritance of the Rh system. Neither of the two principal hypotheses has difficulty in disposing of the new factor.

Multiple allele hypothesis. The proponents of the hypothesis originated by Wiener[20] consider the antigen f as being part of the antigen mosaic usually determined by the genes r and R^0 in the same way that the antigens hr′ and hr″ are determined by these two genes. It appears that three new symbols will have to be introduced into Wiener's system of nomenclature. The new antigen falls into the category of Hr antigens and the designation hr‴ for this antigen would be consistent. Two new symbols are required to differentiate the alleles of r and R^0 that are not associated with the presence of the new antigen, and it is tentatively suggested that these alleles be distinguished by a small superscript ϕ (phi) so that the symbols R^ϕ and r^ϕ would connote the presence of those variants of the genes R^0 and r that fail to produce the antigen hr‴.

Linked-gene hypothesis. Rosenfield et al.[3] derived the name of the new factor from the fact that they could readily explain its inheritance by postulating a new locus with a pair of allelic genes, Ff, in addi-

tion to the well known pairs Cc, Dd and Ee. The strength of this theory lies in its logical extensions. It would not be expected that the close association of ce and f would be invariable: chromosomes of Type cdeF and cDeF would be predicted as well as chromosomes such as CDef. Furthermore, the theoretical existence of an anti-F antibody is necessary to the hypothesis, and its characteristic reactions may be forecast. It would, in fact, behave like a mixture of anti-C and anti-E with neither component capable of being separated from the other by absorption. Finally, the existence of a fourth locus would materially increase the chances of finding an example of crossing over, which is necessary to the incontrovertible proof of the linked-gene hypothesis.

Position-effect hypothesis. This hypothesis, which is a modification of the linked-gene theory, was suggested by Dr. Arthur G. Steinberg, geneticist at the Children's Cancer Research Foundation of the Children's Medical Center, Boston. In principle, it is based on a phenomenon noted in drosophila,[21] in which the interaction of two genes on the same chromosome gives rise to a characteristic phenotype in the organism. If either or both of these genes are absent or represented by an allele the characteristic phenotype does not appear.

To explain the f antigen in man the theory states that when the genes c and e are together on the same chromosome they interact to produce the f antigen in the red cells. If either of these loci carries the alleles C or E the interaction does not take place, and the f antigen is not produced. It seems improbable that this theory can ever be directly proved, but certain predictions can be made from it. One is that the antigen will never occur when the ce combination on the same chromosome is broken. Another is that F and anti-F do not necessarily exist, and a third is that even minor alterations of one or the other of the c or e loci may bring about the absence of f from the cells. This last prediction was made in a previous communication with little hope of its being fulfilled, but supporting evidence accumulated since then is being presented elsewhere. This evidence consists of data obtained from a study of the Rh genotypes through three generations of a family. It was possible to identify in each generation the very unusual chromosome $c^{v}De$ and to show that this chromosome failed to confer on the red cells the property of reacting with anti-f serum. The data were interpreted as supporting the prediction that the disturbance of the ce-gene combination by substitution of an allele at the c locus would result in the absence of the f antigen. In this case the substitution of the gene c^{v} for c resulted in only a minor alteration of the serologic properties of the cells, but the f antigen did not appear in the red cells. Against the hypothesis it must be said that it lacks precedent, no indubitable example of position effect having yet been demonstrated in man or in any other mammal.

(*To be concluded*)

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MEDICAL INTELLIGENCE

TOTAL IODINE IN THE EVALUATION OF SERUM PROTEIN-BOUND IODINE

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BOSTON

DETERMINATION of the protein-bound iodine of serum is of value in the diagnosis of thyroid disease only if no iodine in any form has been administered for some time before the test.

In modern medicine iodine is given in many ways and for various reasons. Since this iodine may give falsely high values for the protein-bound iodine, it is essential to know if iodine has been given before the protein-bound iodine was measured. Lugol's solution, potassium iodide, cough mixtures and so forth are the chief offenders. Contrast mediums used in examination of the gall bladder and Lipiodol may increase the value for one or two years, and pyelograms for a week or two.

It was recently found that, by determining the total iodine of the serum along with the protein-bound iodine, one can readily ascertain if a patient has been free of excess iodine. When there is no iodine contamination, the total iodine is the same or only slightly higher than the protein-bound iodine (by not more than 1 or 2 microgm. per 100 cc.). On the other hand, if a patient has had inorganic iodine in some form or other, there will be a greater difference between the total iodine and the protein-bound iodine. Radio-opaque mediums, which contain iodine in organic combinations, render both the total iodine and the protein-bound iodine erroneously high, sometimes over 20 microgm. per 100 cc.

Out of the 316 determinations made over the past few months on the general run of specimens sent to the Boston Medical Laboratory, 50 per cent had total iodine levels within 2 microgm. per 100 cc. of the protein-bound iodine. If one considered as much as 3 microgm. per 100 cc. a difference, this value would be raised to 62 per cent. In other words, at least 38 per cent of the specimens had a greater differential than 3 microgm. per 100 cc., possibly owing to contamination. It is therefore important to know the differential of total iodine and protein-bound iodine for proper evaluation of the protein-bound iodine.

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AN EARLY APPENDECTOMY

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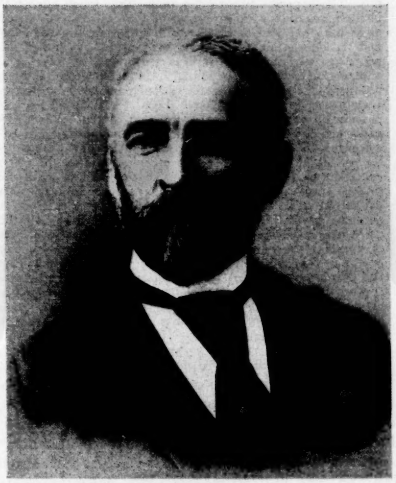
THE opening of the excellent exhibit on appendicitis at the Boston Museum of Science last fall called attention to the history of this disease and brought about considerable discussion of the first appendectomy.

The desirability of early operation was a slowly evolving concept, as recently indicated by MacCallum,[1] whose Dr. Rochester seemed to favor early surgical treatment in the 1850's. Many descriptions of what is now known as appendicitis were presented in the earlier literature. Dr. Benjamin Spector[2] states that the first case of localized appendicitis on record in which operation was performed was reported by Mestivier,[3] that James Parkinson[4] first recognized the perforation of the appendix as a cause of death and that the first recorded successful operation to relieve spreading peritonitis was by Henry Hancock.[5] It is said that Willard Parker[6] was the first American to operate for appendicitis, in 1864, but technically he drained an abscess instead of performing an appendectomy. For



Edward Rowland Cutler

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another quarter of a century this was the usual surgical procedure, while clinical discussion gradually developed on the merits of early versus late drainage of these abdominal abscesses.

In 1886 Reginald Heber Fitz[7] conclusively demonstrated the pathology of the disease and invented the term *appendicitis*. He suggested that the diagnosis could and should be made, and that much earlier operations should be performed, basing his insight on pathological observation and knowledge. But Fitz was a pathologist, and it still remained for the practicing doctor to make the diagnosis, to operate and to cure the patient by cleanly removing the inflamed appendix.

Such an operation was performed in Waltham, Massachusetts, on December 21, 1887, by Edward Rowland Cutler. He later reported the case in the *Boston Medical and Surgical Journal*,[8] as follows:

> Case XI. S. C. W., station agent. Dec. 21, 1887. Violent pain in right inguinal region, with tenderness, vomiting, and fever, but absolutely no physical sign. Laparotomy at end of forty-eight hours. A little turbid serum escaped, but no pus. The appendix was readily found and drawn out at the incision, together with a portion of the caecum. It was not more than one and one half inches long, swollen quite hard and standing straight out from the caecum, which was likewise intensely inflamed. It was perforated at two points adherent to a contiguous coil of intestine, gangrenous superficially and exceedingly friable through its whole substance. Its mucous lining was red and thick. I could find no communication between its lumen and that of the caecum. The peritoneal investment of all the adjacent parts was deeply congested. The appendix was cut off near the caecum and its peritoneal surfaces rolled together as well as the brittle condition of the stump would permit and fixed by a continuous suture of fine catgut. Drainage for a few days. The patient left town in just two weeks, and remained well at last accounts several months after operation. I have said that the last case may *seem* to be an exception in a group of cases of purulent peritonitis, but when it is remembered that the operation was done in forty-eight hours from the first pain, and that a perforated, intensely inflamed, and even gangrenous appendix lay almost free in the abdominal cavity, I think that no one can doubt that in forty-eight hours more we should have had an abundance of adhesions and pus in place of simple redness and turbid serum.

The last sentence of this account indicates how little Dr. Cutler was concerned with the idea of priority; indeed, he all but apologized for including S.C.W. in his little series of 11 cases. If an earlier, documented example of such a clean-cut appendectomy can be claimed it should be presented. From 1887 on, the indications for early operation were well understood and acted upon by Dr. Cutler and his associates, especially Alfred Worcester.[9-14] Still, as late as 1893, according to Cushing,[15] "appendicitis was still largely regarded as a medical disorder."

Cutler was born January 15, 1840, in Boston. After two years of premedical study at Williams College he entered Harvard Medical School in 1860. He received the degree of M.D. in 1863. On the day of his graduation he walked directly from the Medical School to the State House, where he enlisted in the medical corps and was commissioned an assistant surgeon in the Union Army. He was said to have rendered distinguished service in combat. In April, 1864, he married Melvina Amanda Rogers at Washington, D. C. During 1865 and 1866 he engaged in the practice of medicine in Hartford, Connecticut. He used to say that it was there he found out that he "didn't know anything" and so determined to spend three years of study in Europe. Returning from Vienna in 1870, he settled in Waltham, where he remained in vigorous general practice until he retired in 1906. Dr. Cutler was said to have been an unceasing reader of medical literature, and for many years after his retirement he completely read each daily issue of the *New York Times*. He died on September 24, 1924. Several physicians still living remember him well.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 40071

PRESENTATION OF CASE

First admission. A sixty-nine-year-old retired salesman was admitted to the hospital because of diarrhea and vomiting. Six hours before admission, while he was watching a bowling match, a non-radiating pain developed in the midepigastrium and left anterior portion of the chest, associated with nausea and vomiting, and loose watery stools. About once a week for the past ten years dull precordial pain had occurred after exertion or heavy meals; the pain radiated down the left upper arm and was relieved by rest or aspirin.

Physical examination showed a well developed and well nourished man. The pupils reacted to light and on accommodation, the neck veins were flat and the chest was clear. The point of maximal cardiac impulse was in the fifth intercostal space 2.5 cm. to the left of the midclavicular line. There was a loud, grating, rough, Grade 2 to 3 aortic systolic murmur transmitted to the neck and over the precordium. A Grade 2 to 3 aortic diastolic blow was heard best along the left lower sternal border. The rhythm was regular. There was a Corrigan pulse; capillary pulsations were noted. The remainder of the examination was negative.

The temperature was 103°F., the pulse 90, and the respirations 20. The blood pressure was 130 systolic, 40 diastolic.

The urine had a specific gravity of 1.018 and was normal except for the sediment, which contained 4 or 5 white cells and 3 or 4 granular casts per high-power field. Blood studies revealed a hemoglobin of 15 gm. per 100 cc. and a white-cell count of 17,600, with 92 per cent neutrophils. A blood Hinton test was positive. A stool gave a + guaiac reaction. Stool culture was negative for pathogens. An electrocardiogram showed nonspecific T-wave changes that did not vary on subsequent tracings. A chest roentgenogram disclosed clear lung fields and a heart shadow of normal size and shape. The cardiothoracic ratio was 11.5:28.

The temperature returned to normal in twelve hours, and he remained asymptomatic thereafter. He was discharged on the seventh hospital day.

Second admission (two weeks later). He was admitted to the hospital for penicillin therapy for syphilis. The physical examination and laboratory studies were unchanged. The cerebrospinal-fluid findings on lumbar puncture were normal, with a negative Hinton test. He was given 40,000 units of penicillin every three hours for a total of 6,000,000 units and then discharged.

Third admission (three and a half years later). In the interval he had been active and was able to climb stairs without excessive dyspnea, ankle edema or orthopnea. Eighteen hours before admission while sitting listening to the radio he noted a sudden severe pain in the anterior part of the chest that did not radiate and was not increased by respiration. The pain was steady and dull, with exacerbations every one or two hours, and lasted two to five minutes. He was apprehensive and orthopneic but he denied palpitations.

New positive physical findings included atrial fibrillation (rate of about 170 per minute) and scattered moist rales at the lung bases. The remainder of the physical examination was unchanged.

The temperature was 99.2°F., the respirations 24, and the blood pressure 140 systolic and 50 to 0 diastolic.

The urine had a sediment containing 2 or 3 white cells per high-power field but was otherwise normal. The blood hemoglobin was 15 gm. per 100 cc., and the white-cell count 10,200, with 84 per cent neutrophils. A stool guaiac test was negative. The serum nonprotein nitrogen was 34 mg., and the fasting blood sugar 88 mg. per 100 cc. After 0.8 mg. of Cedilanid had been given the cardiac rhythm reverted to normal, and the patient became asymptomatic. Subsequent electrocardiograms were similar to the one taken three years earlier. He was discharged to continue with digitoxin and salt restriction.

Fourth admission (fourteen months later). Since the last discharge, he had continued to take digitoxin, 0.1 mg. daily; however, he had been moderately dyspneic on exertion and had orthopnea requiring 2 pillows for relief but no ankle edema. About two or three months before admission he had noted the onset of mild, gnawing epigastric pain associated with weakness. The pain had been more or less constant, was relieved temporarily by the taking of milk or soup and was unassociated with other gastrointestinal symptoms. The weakness, however, became increasingly more severe, and the weight had fallen from 158 to 110 pounds. He denied having fever, chills or sweats.

On physical examination the patient was emaciated and appeared chronically ill. There were a few small axillary lymph nodes; the skin, eyes, mouth and neck were normal. The lungs were clear, and the heart had an easily palpable systolic apical thrill. There was a blowing, Grade 3 aortic systolic murmur and a harsher, Grade 3 systolic blow at the apex. A short, Grade 2 soft diminuendo diastolic blow was heard in the right second intercostal space. The aortic second sound equaled the pulmonic, and the rhythm was regular. Corrigan pulses were present.

The temperature was 100.6°F., the pulse 90, and the respirations 22. The blood pressure was 140 systolic, and 50 to 0 diastolic.

The urine had a specific gravity of 1.011 and gave a + test for albumin; the sediment was loaded with red cells and contained 2 to 4 white cells per high-power field but no casts. In subsequent urinalyses one specimen contained 50 red cells per high-power field, and a second was again "loaded" with red blood cells. The hemoglobin was 9.8 gm. per 100 cc., the hematocrit 21 per cent, and the white-cell count 11,800, with 89 per cent neutrophils. The red cells were small and hypochromic. The serum total protein was 6.1 gm., the albumin 2.7 gm., the globulin 3.4 gm., the nonprotein nitrogen 54 mg., and the serum iron 150 microgm. per 100 cc. The bromsulfalein retention was 18 per cent on admission and 5 per cent nine days later; cephalin flocculation was +++ in forty-eight hours. A guaiac test on a stool was negative; a urine culture grew out *Escherichia coli.* Another film of the chest revealed congestive changes and bilateral slight pleural effusion. A gastrointestinal series demonstrated two small, rounded filling defects in the body of the stomach. An intravenous pyelogram was normal; cystoscopic examination showed enlargement of the lateral lobe.

During the four weeks before operation there were daily temperature rises to 100°and to 101°F. on two occasions. Four 500-cc. blood transfusions were given, after which a gastrotomy was performed, with the removal of two benign polyps. The stomach was otherwise normal. Postoperatively, a temperature of 101°F. developed, and the white-cell count was 16,500, with 97 per cent neutrophils. The patient was treated with crystacillin, 300,000 units twice a day for seven days, with a fall of the temperature; x-ray examination disclosed clearing of a vague rounded density behind the heart in the posterior costophrenic sulcus. The heart was again noted to be small in the x-ray films. A sputum culture grew out alpha-hemolytic streptococci, pneumococci and *Haemophilus influenzae.* He was discharged on digitoxin, a bland diet and crude liver extract on the twenty-fourth postoperative day.

Final admission (one month later). Since discharge from the hospital he had been up and about in the house and felt slightly better; two days before admission he had a severe nosebleed, which required packing. On the next day, while in bed, he noted severe pain in the anterior part of the chest, radiating down the left arm. "After some time" he coughed up blood, and the pain subsided; however, it returned twelve hours later, and he was admitted to the hospital. The pain was greatly relieved by nitroglycerin.

On physical examination the patient was pale and wasted but in no acute distress. The neck veins were flat. There were bilateral basal and axillary wet rales. The heart was believed to be enlarged, the border extending to the midaxillary line; the rhythm was regular, and the aortic second sound equaled the pulmonic. A harsh, Grade 2 systolic murmur was heard at the base and apex, and a Grade 2 diastolic murmur along the sternal border, base and apex. There was no gallop. The liver edge was palpated one fingerbreadth below the right costal margin, and there was ++ ankle edema.

The temperature was 98.6°F., the pulse 90, and the respirations 24. The blood pressure was 110 systolic and 20 to 0 diastolic.

The urine had a specific gravity of 1.005 and gave a trace test for albumin; the sediment contained 50 white cells, 2 to 4 red cells and occasional casts per high-power field. Examination of the blood revealed a hemoglobin of 6.5 gm. per 100 cc. and a white-cell count of 10,100, with 68 per cent neutrophils, 29 per cent lymphocytes and 3 per cent monocytes. Repeated stool guaiac tests were negative. The bleeding time, clotting time and platelet count were normal; a Coombs test was negative. The total protein was 5.8 gm., the albumin 3.0 gm., the globulin 2.8 gm., the bilirubin 1.4 mg., and the nonprotein nitrogen 52 mg. per 100 cc. Bone-marrow aspiration showed normoblastic hyperplasia. An electrocardiogram was unchanged. A roentgenogram of the chest disclosed a soft, fluffy, symmetrical infiltrate in both perihilar areas and slight congestion of the pulmonary vessels.

The patient was given two transfusions, and after nine days a bilateral ligation of the superficial femoral veins was done but no clots were found in the veins nor was there any swelling of the legs. On the thirteenth day the nonprotein nitrogen was 92 mg. per 100 cc. Five blood cultures in paired flasks were drawn with alpha-hemolytic streptococci growing from a single flask and *Staphylococcus albus* from another single flask. Urine cultures grew out abundant *Esch. coli.* He slowly became weaker and less responsive and was difficult to maintain nutritionally. The highest white-cell count recorded was 12,000, and the temperature curve was persistently irregular, ranging from normal to 100°F. He died on the twenty-third hospital day.

Differential Diagnosis

Dr. Walter Bauer*: "A blood Hinton test was positive." Were the physicians not able to obtain a history of a primary infection? Was the blood Hinton test repeated during any of the later admissions? My question is, Did the physicians interpret the cardiac findings as being manifestations of syphilis?

Dr. Benjamin Castleman: The patient had a history of a penile sore twenty-five years before the first admission; at that time he was treated for gonorrhea. Two years before the first admission he had a positive blood Hinton test and was given 18 injections of bismuth. During the first admission the blood Hinton test was positive, but during the second admission, the test had become negative.

Dr. Bauer: "The aortic second sound equaled the pulmonic and the rhythm was regular. Corrigan pulses were present." There was no indication that the aortic second sound was louder than the pulmonic at the time of the first physical examination.

At the time of the first admission this man had a history of angina for ten years, evidence of aortic insufficiency and a positive blood Hinton test. During the second admission he was treated for syphilis; whether or not he was so treated because the physicians interpreted the findings as representing syphilitic heart disease is not indicated. I hesitate to make a diagnosis of syphilitic heart disease because of the ten-year history of angina. I assume that one might argue that, in addition to syphilitic heart disease, this patient had symptomatic coronary-artery disease, thereby accounting for the angina on a nonsyphilitic basis. I wish to emphasize, however, that it is most unusual for a man with angina pectoris as a symptom of syphilitic heart disease to have no more trouble than this for ten years. Do you agree, Dr. Friedlich?

Dr. Allan L. Friedlich: Yes.

Dr. Bauer: The problem on the third admission was to explain the severe pain in the anterior part of the chest that the patient experienced while sitting; it will be remembered that there was no radiation to the left arm as there had been with the previous attacks of chest pain. I shall assume that, with the onset of fibrillation in this man with coronary-artery disease, pain ensued because of coronary insufficiency without myocardial infarction; however, the pain may have been due to pulmonary embolism. I think it likely that he had calcareous disease of the aortic valve at this time. The fibrillation and congestive heart failure responded to the treatment given, and evidently he remained well for quite some time.

At the time of the fourth admission this patient obviously had something else besides the lesion that was treated surgically. The hemoglobin was only 9.8 gm. per 100 cc.; yet the stools — I assume that a number were examined — gave negative guaiac tests, indicating that the anemia was not due to blood loss. Other abnormalities noted at this time included the urinary findings, a low serum albumin, an elevated serum globulin, a nonprotein nitrogen of 54 mg., bromsulfalein retention of 18 per cent on one occasion and 5 per cent on another and +++ cephalin flocculation. On the basis of these findings I think it is fair to assume that this man, who had gastric polyps that were successfully removed, was ill with some other disease throughout this hospital stay. Additional information favoring this interpretation is the postoperative temperature of 101°F., or higher, and a white-cell count of 16,000, with 92 per cent neutrophils. With the administration of penicillin the fever disappeared, and there was clearing of the "vague rounded density behind the heart in the posterior costophrenic angle." Whether or not the density was a pneumonitis, an acute lung abscess or a pulmonary embolus, I cannot establish. Perhaps when we see the films we shall learn what the radiologists found.

On the last admission there was a history of a nosebleed while he was sitting in bed and a recurrence of severe chest pain that radiated down the left arm. The pain, I think, is explained best on the basis of coronary-artery disease. Upon coughing up blood he was relieved; however, the pain returned twelve hours later and, as was stated, was relieved by nitroglycerin. I hesitate to make a diagnosis of pulmonary embolus though I am well aware of this possibility. I prefer to attribute the pain to coronary insufficiency. On this occasion he had even more anemia than on the previous admission; yet the guaiac tests were again negative. This time the bilirubin was 1.4 mg. per 100 cc.

I believe all these findings indicate the presence of calcific disease of the aortic valve — a diagnosis I prefer to syphilitic heart disease — and a superimposed subacute bacterial endocarditis, with focal nephritis and focal liver damage. Certainly, the renal and hepatic abnormalities observed would be in keeping with this diagnosis. Whether there was a pyelonephritis in addition I cannot say.

If this man had subacute bacterial endocarditis, what organism caused it? I should like to think it was a *Staph. aureus* infection, which might explain the "vague rounded density" posterior to the heart that disappeared with the administration of the penicillin. The bacteriologic studies certainly were not helpful in that the staphylococcus isolated was a *Staph. albus* and not a *Staph. aureus*. An infection with the latter organism would explain the high white-cell and neutrophil counts observed during the last two hospital admissions. My diagnosis, on the other hand, leaves certain things unexplained, particularly the soft, fluffy infiltrate noted in the chest films during the last hospital stay. I believe

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that this was nothing more than edema due to congestive heart failure; if it really was an infiltrate I am wrong.

What other conditions might this patient have had? I cannot think of many. The findings reported are best explained on the basis of a staphylococcal endocarditis with intermittent bacteremia. There is, of course, the possibility of a pylephlebitis after the operation, but since the history is not consistent with this diagnosis I shall dismiss it.

My final diagnosis is calcareous disease of the aortic valve, with a superimposed subacute bacterial endocarditis. I believe that the organism was a *Staph. aureus*. There was associated focal nephritis and focal liver damage. I prefer to interpret the first pulmonary lesion as being infectious and not due to a pulmonary embolus and the "bilateral soft fluffy infiltration" as being pulmonary edema due to congestive heart failure.

The thing that impressed me as I read this record was the absence of cardiac enlargement. Did the x-ray films show any elongation or widening of the lower portion of the aorta? May I see them?

DR. JOHN F. GIBBONS: On this film, apparently taken at the time of the first admission (five years before the last admission), the heart is quite small; the lungs are moderately emphysematous. There is pleural thickening at the apexes and the right costophrenic angle. In the films taken a year and a half later there is no real change. In the films at the time of the third admission, when the patient was treated with Cedilanid, the heart looks slightly larger than before, and there is fluid in the right major fissure and some fluid in the right costophrenic angle. The aorta has not changed in contour, and the heart is certainly not much enlarged. The vague, rounded shadow behind the heart that was mentioned at the time of the fourth admission and disappeared after forty-eight hours can be discounted, I think. The film is not a true lateral film, and we know that the patient had pleural thickening and had had fluid in that area so that I believe the radiologists were looking at thickened pleura on two sides of the bases of the lung and partly at the chest wall in a somewhat oblique film. In a true lateral film, taken a couple of days later, that shadow has disappeared. Again, we note the thickened pleura posteriorly. There is certainly nothing in the parenchyma of the lung. At this time the heart is again small, and there is no congestive change. The aorta looks the same; the carina looks normal. At the time of the final admission, a month later, fluffy mottled densities have developed in both lungs. The heart is still not very large, although there is elevation of the left main-stem bronchus that progressed as the heart became larger, suggesting enlargement of the left atrium, which would go along with the enlargement of the other chambers. There was also a more or less solid density in the upper lobe on the right side and a lesser degree of consolidation of the left upper lobe. The heart during the last admission became larger. As the size of the pulmonary vessels increased progressively more density developed in both lungs, with an almost solid density in the right upper lobe, which raises the question of bronchopneumonia versus infarction of the right upper lobe. Most of the changes from my standpoint could be explained on the basis of heart failure with superimposed bronchopneumonia and probably pulmonary edema. I think it is impossible to say how much is pneumonitis and how much is edema at the end.

DR. BAUER: I failed to mention the possibility of a bicuspid aortic valve. I think I shall leave it that the patient had either calcareous disease of the aortic valve or a bicuspid aortic valve, superimposed subacute bacterial endocarditis with focal nephritis and focal liver damage due to *Staph. aureus* and coronary-artery disease. He may have had some pyelonephritis, and he obviously had congestive heart failure.

Dr. Friedlich, would you be reluctant to make a diagnosis of syphilitic heart disease?

DR. FRIEDLICH: It would be much more likely to be rheumatic heart disease or a congenital bicuspid valve, with or without calcareous changes superimposed.

DR. CASTLEMAN: How often does one observe a Corrigan pulse with rheumatic or calcareous stenosis of the aortic valve?

DR. FRIEDLICH: If there are extensive calcareous changes the stenosis is occasionally sufficiently severe so that there is not much regurgitation. Certainly, there may be perfectly free aortic regurgitation from rheumatic heart disease.

DR. BAUER: If aortic stenosis was that severe would you not expect him to have had much more cardiac enlargement?

DR. FRIEDLICH: Yes, indeed.

DR. BAUER: I should have expected it to be present at the time of the first admission as well as four and a half years later.

DR. FRIEDLICH: Free aortic regurgitation occurs on the basis of congenital bicuspid valves that have been further damaged by subacute bacterial endocarditis. Another thing that I should worry about is whether this was *Streptococcus faecalis*.

DR. BAUER: I meant to mention that, because some of the historical findings suggest this organism. Whatever the organism, it seemingly was penicillin sensitive because with its administration the temperature returned to normal postoperatively.

DR. CASTLEMAN: Does everyone agree that there was a bacterial endocarditis?

DR. MARIAN W. ROPES: That would be my choice.

DR. MYLES P. BAKER: I was on the service the last two weeks of this man's life. I was not aware that fever was prominent. The prominent symptom

during the last two weeks was the spitting up of blood, without mucopurulent material.

DR. BAUER: That was mentioned only once in the whole history.

DR. FARAHE MALOOF: Dr. Gibbons, does the pericardium look irregular?

DR. GIBBONS: No; I do not think so. Most of the irregular contour that appears along the left border is probably engorged main branches of the left pulmonary artery and is in the lungs rather than in the pericardium.

DR. BAUER: Dr. Friedlich, which do you favor — syphilitic heart disease or rheumatic heart disease?

DR. FRIEDLICH: I think I should favor either rheumatic heart disease or a bicuspid aortic valve.

DR. CASTLEMAN: Are you going to ignore the definite history of syphilis?

DR. BAUER: If the patient had had angina due to syphilitic heart disease when first seen, I should not expect him to have lived so long.

DR. FRIEDLICH: I think that is true.

DR. ALFRED KRANES: One has to keep in mind that atherosclerosis is common in the presence of syphilis and that the angina may have been due to the coronary-artery disease, not to the syphilis.

DR. FRIEDLICH: He could have had arrested syphilitic heart disease and an entirely independent lesion.

DR. BAUER: For the patient to have lived over four years after the onset of atrial fibrillation and congestive heart failure would be most unusual in syphilitic heart disease.

DR. KRANES: I used to believe that, Dr. Bauer, but I do not any more.

DR. BAUER: I think we shall make fewer mistakes in prognosis if we think of this patient as an exception if he had syphilitic heart disease.

DR. JACOB LERMAN: On all the previous admissions, a diagnosis of syphilitic heart disease was made by the service.

CLINICAL DIAGNOSIS

Syphilitic heart disease.
?Rheumatic heart disease.

DR. WALTER BAUER'S DIAGNOSES

Calcareous aortic stenosis or bicuspid aortic valve, with superimposed subacute bacterial endocarditis.
Coronary-artery disease.
Focal nephritis and focal liver damage.

ANATOMICAL DIAGNOSES

Syphilitic aortitis, with aortic insufficiency.
Rheumatic heart disease, with mitral disease.
Subacute bacterial endocarditis, with rupture of aortic and mitral valves.
Hemorrhagic bronchopneumonia.
Central necrosis of liver.
Acute glomerulitis.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The diagnosis of syphilitic heart disease started with Dr. J. Howard Means on the first admission, and that is what the patient had. That, however, was not all he had. The ascending aorta had the stellate scars quite characteristic of syphilitic aortitis and also the classical separation of the cusps at the commissures allowing for free regurgitation. The aorta above the valve was dilated to 10 to 12 cm. in circumference. The heart was large and dilated, weighing 630 gm. There was marked flattening of the trabeculae carneae of the left ventricle, indicating a long-standing aortic regurgitation.

FIGURE 1. *Opened Left Ventricle, Showing Flattening of Trabeculae Carneae, Syphilitic Aortitis and Bacterial Endocarditis. Arrow points to string in the perforated aortic cusp.*

One of the coronary mouths was perfectly free; the other was slightly impinged upon by the arteriosclerosis that was superimposed on the syphilitic aortitis. I should not have supposed that he could have had anginal attacks from this degree of occlusion of the mouths of the coronary arteries. The coronary arteries themselves were not remarkable; the left was clear, and the right had only an occasional atheromatous plaque.

Dr. Bauer was correct in the diagnosis of subacute bacterial endocarditis. On the aortic cusps were vegetations, some of which were slightly calcified and one of which was perforated (Fig. 1). On microscopical examination the vegetations contained

organisms, some of which had calcified. Calcification is not uncommon in healing or long-standing subacute bacterial endocarditis, and therefore the bacterial endocarditis had probably been present for some time. Although it is unusual for bacterial endocarditis to develop on a syphilitic aortic valve, I think that occurred here. The other possibility is that there was an element of rheumatic involvement in addition to the syphilis. The cusps of the aortic valve were only slightly thickened, but the thickening was sufficient to bring up the possibility of rheumatic involvement especially since the

FIGURE 2. *Rheumatic Involvement of the Mitral Valve. Arrows point to the thickened and ruptured chordae tendineae involved with bacterial endocarditis.*

mitral valve showed definite rheumatic involvement (Fig. 2). The chordae tendineae of the mitral valve were not only thickened and calcified but also ruptured owing to the bacterial endocarditis, the free edges being granular and rounded. One leaflet of the mitral valve was very thick; the other was perhaps slightly thickened, but there is no doubt that there was old rheumatic mitral disease with a superimposed bacterial endocarditis.

To go back to the aortic valve disease, the basic lesion that had caused the aortic insufficiency over the years was undoubtedly the syphilitic aortitis with the separation of the cusps. If mitral disease had not been found the diagnosis of a subacute bacterial endocarditis engrafted on a syphilitic valve would not be questioned, and I still prefer to regard it as such, admitting the possibility, however, of an additional mild, chronic rheumatic lesion on the aortic valve.

There was a severe hemorrhagic bronchopneumonia; blood throughout all the alveoli explains why the patient was spitting it up. There was no evidence of infarction or emboli anywhere. The liver had quite severe central necrosis, with many polymorphonuclear leukocytes; the necrosis was very active and, I think, was due to mild heart failure and the superimposed bacteremia. The collecting tubules of the kidneys contained some blood and the tufts showed mild but definite changes of a glomerulitis such as we sometimes see with a bacterial endocarditis. There was no pyelonephritis.

DR. BAUER: What was the organism?

DR. CASTLEMAN: The post-mortem blood cultures were negative. Under the microscope the organisms looked like streptococci so that I believe the alpha-hemolytic streptococci that were grown on one of the cultures were probably the ones we should choose.

DR. BAUER: This man was fortunate to have lived four and a half years after the onset of congestive heart failure if he had both syphilitic and rheumatic heart disease.

DR. FRIEDLICH: How do you suppose he acquired the subacute bacterial endocarditis?

DR. CASTLEMAN: He may have had pneumonia on the third admission.

CASE 40072

PRESENTATION OF CASE

A twenty-three-year-old housewife was admitted to the hospital for study of infertility. She stated that she had been married for two and a half years and had been unable to become pregnant.

Menstruation had begun at the age of twelve, with periods beginning every twenty-eight days and lasting seven to eight days. The flow was described as moderate without clots. She had cramps for one day at the beginning of each period. Bleeding became irregular at the age of fifteen and had been irregular ever since. The bleeding pattern, which had been constant for the year and a half before admission, was a period of flow for five or six days, no flow for seven days, then another flow for five or six days and so forth. She did not have cramps. During the past year she had been under the care of a physician. Basal-body-temperature charts showed no ovulatory pattern. Because of a "slightly minus" basal metabolic rate, she was given thyroid hormone until four months before admission. She was also given progesterone and estrogen therapy of unknown dosage without effect. Dilatation and curettage were performed a year before admission; however, the results were not known. The husband's sperm count was normal, with many active forms.

The past history was irrelevant except for tonsillectomy and appendectomy. There was no known change in hair distribution. She had never lived with her parents but had been brought up by a number of foster parents, with most of whom she had been unhappy.

Physical examination showed a well developed and well nourished woman. The breasts were well developed, and the hair on the body was normal in quantity and distribution. There was a small, well healed scar in the right lower quadrant of the abdomen. The uterus was anterior and was normal in size; the vaults were normal except for a questionably palpable left ovary. The rest of the examination was negative.

The temperature was 98.6°F., the pulse 80, and the respirations 20. The blood pressure was 120 systolic, 80 diastolic.

Urinalysis was negative. Examination of the blood disclosed a hemoglobin of 12.6 gm. per 100 cc.; a single white-cell count was 5800, with 56 per cent neutrophils, 34 per cent lymphocytes, 2 per cent monocytes and 7 per cent eosinophils. The blood sugar was 76 mg. per 100 cc. The blood Hinton test was negative, as was a vaginal smear. The basal metabolic rate was –1 per cent. The 17-ketosteroids were 8.4 mg. per twenty-four hours; the FSH (follicle-stimulating hormone) was positive for 6.5 mouse units, slightly positive for 13 and 52 mouse units and negative for 104 mouse units per twenty-four hours (normal, 6.5 to 26 mouse units per twenty-four hours).

Culdoscopic examination showed the left ovary to be two or three times the size of the right. The ovaries were pale white and smooth, with thick capsules. There were prominent vessels on the surface and a suggestion of cysts beneath the capsule. The uterus was small, and the tubes normal. No endometriosis was seen. There were a few filmy adhesions about the tubes and ovaries, more on the right side than on the left.

On the fourth day an operation was performed.

Differential Diagnosis

Dr. Somers H. Sturgis*: I should like to go back over this protocol briefly and pick out a few data to comment upon before considering any diagnoses. In the first place I think I can assume that for the first three years after the menarche at the age of twelve, when the periods were regular with crampy flow, the patient was probably having normal ovulatory periods and normal ovarian function. It was not until eighteen months before admission that she started to have the irregular pattern that strongly suggested anovulatory flow; the temperature chart then gave no evidence that ovulation had occurred. The periods that she had for a year and a half before admission certainly suggest that the ovaries were excreting estrogen. I have to assume, however, that estrogen production was inconstant, sometimes being high in the blood owing to a number of follicles developing at one time but failing to ovulate and becoming atretic, and then being low with an estrogen-withdrawal type of bleeding producing a flow lasting six or seven days.

She was given progesterone and estrogen without effect. I do not know the dosages. Actually, if the previous statement of mine is correct, she did not need estrogen: she was producing estrogen all the time. I should have been inclined to give progesterone cyclically for three or four days a month and to repeat this every three weeks; I should not have believed that she needed estrogen since I interpret this story as that of persistent estrogen formation.

She had a dilatation and curettage a year or so before admission, the result of which is not known. I think a reasonable assumption from this negative statement is that she did not have carcinoma of the endometrium over a year before admission.

In the past an appendectomy had been done. We are not told when, or whether the appendicitis was acute. The small scar probably means that the appendix had not ruptured. It would have been helpful if the surgeon at the time of appendectomy had done a midline incision and looked at the ovaries. This small scar did not give the operator a chance to see what the ovaries were like.

The uterus was normal in size, as I should expect if estrogen was constantly being produced. I was thinking last night that the statement that the vaginal smear was negative, which is well understood by all of us, might be confusing in 2000 A.D. if by that time there is a nice easy serum test for cancer and Papanicolaou smears are no longer done for that reason. Somebody then might well ask, Negative for what? Negative for progesterone, negative for estrogen, negative for trichomonas? Although we all know what it means, the statement is ambiguous.

The 17-ketosteroids of 8.4 mg. in twenty-four hours is in the average range for a woman of this age; only one test was done. The FSH test was slightly positive for 13 and 52 mouse units. Anyone who is familiar with the difficulties of interpreting the response of weanling mice in the FSH test would be sympathetic with my view that the slightly positive test for 52 mouse units does not mean that that is necessarily an elevated FSH level. Indeed, it would be inconsistent with the statement already made about the constant estrogen production for a year and a half, which probably would be associated with 6.5 or even 13 or 26 but probably not 52 mouse units. I suspect that the slightly positive test for 52 mouse units can be disregarded.

At the operation, done on the fourth day, the surgeon found the pelvic organs as described on

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culdoscopic examination; he did a wedge resection of the capsule of both ovaries, perhaps encountering a cyst on the left — it might have been a simple follicle cyst. The material that was given to the pathologist was reported as showing a thick tunica albuginea and fibrosis, with some theca luteinization consistent with the Stein–Leventhal syndrome. Those are not facts; they are what I think happened. I am going to deviate from the usual routine of these exercises by "sticking my neck way out" and saying that that was the diagnosis given by the pathologist. Therefore, I shall not discuss any other diagnoses. I shall leave out the possibilities of thecoma, granulosa-cell tumor, dysgerminoma, Leydig-cell tumor and all the other masculinizing tumors because the patient was not masculinized in any way, as well as carcinoma and all other diseases that may have occurred in the left ovary. I shall confine my discussion to the complexities and confusion surrounding the diagnosis of Stein–Leventhal ovaries. That syndrome has us all confused.

Stein[1] considered the clinical characteristics of the syndrome to be menstrual irregularities (especially amenorrhea), a history of sterility, masculine hair distribution, retarded breast development and obesity. He noted that the ovaries, which were similarly and simultaneously enlarged, showed typical cystic changes that were irreversible and refractory to hormone therapy. This condition was not believed to be congenital, inflammatory or degenerative but the result of a definite endocrine disturbance. Leventhal and Cohen[2] described the microscopical features as consisting of a thick and fibrous tunica, and follicles in varying stages of cystic degeneration and development. One of the most consistent findings was marked hyperplasia of the theca interna. Luteinization was frequently noted in this layer.

The treatment has been the wedge resection of the ovaries and puncture of the cysts underneath the capsule. This treatment, according to the reports of Stein,[3] Ingersoll,[4] Meaker,[5] Siegler[6] and Weinstein,[7] resulted in about 65 per cent conception in patients who were married and about the same percentage or slightly higher of return of menstrual function. It should be noted, however, that about 35 per cent of the patients did not respond to this particular treatment.

How can we classify this case as a Stein–Leventhal syndrome? The patient had no amenorrhea, no hirsutism, no retarded breast development and no obesity; she had only one enlarged ovary, and usually both ovaries are equally involved. Are there any precedents for a departure from the classic picture that the literature has given us? Four of Ingersoll's patients had excessive bleeding — menorrhagia rather than amenorrhea — after a period of amenorrhea. Recently, at the Peter Bent Brigham Hospital, we have had 3 patients with ovaries described pathologically as consistent with Stein–Leventhal syndrome on microscopical section. All these had high 17-ketosteroid levels; 2 responded to wedge resection. This morning I received proof that one of them had ovulated, with a positive pregnanediol test. One, however, did not respond and was found at operation to have unilateral adrenal hyperplasia. Jailer[8] recently told the story of seeing on the surgical wards a typical patient with Cushing's syndrome — a fat woman lying in bed with an abdominal dressing — and saying, "What is this Cushing syndrome doing on the surgical ward?" The resident answered, "This is a Stein–Leventhal syndrome; we have operated on her and the ovaries are typical." He went a little farther and noticed a typical adrenogenital syndrome, a large muscular hairy girl and said, "What is this case doing on the surgical ward?" "Oh," was the reply, "this patient has Stein–Leventhal ovaries. We received that report this morning." Obviously, there are patients who do not have one or another of the characteristic features of this confusing syndrome.

Can we establish the etiology of this condition of the ovaries? In all the cases that I have mentioned the common pathological denominator is that the ovaries are smooth and pale, with thick capsules; many cysts are seen beneath the capsules, and possibly thecal luteinization of varying degrees is present. How is this caused? Some years ago Albright[9] postulated the following sequence of events: he thought that, possibly owing to ovulation failure and continuous estrogen production, the pituitary gland was stimulated to release the luteinizing hormone fraction, which had two effects — one on the adrenal cortex, to produce some androgenic corticoid responsible for the hirsutism so often found, and the other on the ovaries, with thecal luteinization and amenorrhea. The only difficulty with this thesis is that the 17-ketosteroid levels in the first cases studied were not elevated. Since that time the levels in some cases have been elevated. Albright's theory, it seems to me, presupposes that the original disturbance was in the ovary. I think it would be equally consistent with his theory of persistent estrogen production for menorrhagia or else periods of amenorrhea followed by excessive flow to occur. Since that would be a condition primarily starting in the ovaries, the wedge resection with destruction of all the follicles producing estrogen might break this cycle and result in a return to normal function.

In 1951 Leventhal and Cohen[2] suggested an alternative possibility, based on Reynolds's[10] finding that the ovaries were nourished by spiral arterioles and that some gonadotropin was released from the pituitary gland to start ovarian follicles along the path of cystic enlargement. Such cystic enlargement would then pull out the spiral arterioles, — they would pay out, as it were, — and the intra-arteriolar pressure would increase with a resultant

transudative edema into the ovaries and eventually into the follicles causing further distention of the ovaries (a vicious circle that could only be relieved by the decompression operation of wedge resection, which would allow the arterioles to shrink back to their original form). This presupposes an original disorder in the pituitary gland.

It seems to me that in trying to explain this complex and confusing clinical picture, which has a single histologic appearance, we are coming perhaps to form an idea that there are two kinds of situations causing the "Stein–Leventhal ovaries." One condition would be primary in the ovary, and in these cases wedge resection would yield good results: the return of menstrual function, the possibility of pregnancy and so on. The other would be secondary in the ovary to either adrenal or pituitary endocrine change; in these cases the wedge resection would not do any good. It would be tempting to say that we can easily differentiate the primary ovarian type from the secondary type by doing steroid assays on the urine, because if the adrenal gland were primarily involved, the ketosteroid level would be high. Unfortunately, we cannot rely on such an easy test. We must remember that the test for ketosteroids as well as for the 11-oxysteroids and the 17-hydroxysteroids is a poor measurement of what is going on in the system. If pituitary stimulation causes excessive adrenocortical production and that particular production is toward the Cushing or glucocorticoid type of excretion, the 17-ketosteroid level will not be elevated. One can speculate whether this patient had an incipient type of Cushing's syndrome without clinical evidence of it. As a rule the glucocorticoids are not broken down into 17-ketosteroids. On the other hand adrenal stimulation by the pituitary gland might result in an excess of the androgenic type of corticoid with an elevation of the ketosteroids. There are a few cases at the Peter Bent Brigham Hospital like that. The ketosteroid assay is not the answer.

In conclusion, I think the problem cannot be solved until we have some better methods of steroid analysis in the urine to differentiate the kind of adrenocortical function that may be occurring in these cases.

I think as yet we have to rely on a much more old-fashioned test — to know whether the picture the pathologist sees is primary or secondary in the ovaries; this test is merely the clinical response to wedge decompression. If the response is favorable, with return of menstrual function, ovulation and pregnancy, I think we can assume that these are primary Stein–Leventhal ovaries; if, on the other hand, like one of our cases and some of those in the literature, the wedge resection is not effective, the ovarian picture must be secondary to pituitary or adrenal change or both. I am going to conclude with that. I should not be a bit surprised to hear Dr. Fennell say that this patient had a thecoma in the left ovary.

Clinical Diagnosis

Stein–Leventhal syndrome.

Dr. Somers H. Sturgis's Diagnosis

Stein–Leventhal syndrome.

Anatomical Diagnosis

Arrhenoblastoma, left ovary.

Pathological Discussion

Dr. Robert H. Fennell, Jr.: Dr. Meigs, will you tell us your impression of this patient's condition and what you found at operation?

Dr. Joe V. Meigs: When I first saw her, I also thought she had the Stein–Leventhal syndrome. At the time Dr. Thomas H. Green examined her with the culdoscope I had a chance to see the ovaries very clearly, and even then I should have said it was the Stein–Leventhal syndrome. I incised the left ovary first because it was the larger of the two. Part of it was yellowish, and I thought it must be an active corpus luteum but that it was a too perfect one. I also did a wedge resection of the other ovary, which was typical of the Stein–Leventhal syndrome. Then I decided that the yellow body on the left must be a tumor. I am not sure whether I did the right thing or not; I shelled the tumor out from the ovary. It

Figure 1.

came out easily like a follicle cyst or endometrioma and left a normal-appearing ovary.

DR. FENNELL: The tumor as we saw it did look like a corpus luteum in that it was small (2 cm.), soft and yellow. The sections showed well differentiated tubules with interspersed cells that had round nuclei and a moderate amount of pink cytoplasm, very typical interstitial cells or Leydig cells such as one sees in the testis (Fig. 1). I want to emphasize the fact that these tubules are lined by cells that are typical Sertoli cells; they have a vesicular nucleus, some of them have a longitudinal fold, and many are vacuolated. This is a typical tubular adenoma of Pick, a tumor that Robert Meyer[11] described and classified as the well differentiated form of arrhenoblastoma.

Why did this patient bleed? One could suppose, and this has happened in a number of patients with masculinizing arrhenoblastoma, that with the beginning of the hormonal upset they would have periods of excessive bleeding. As a matter of fact Pick's original patient, according to Teilum,[12] had that symptom at the onset of masculinization; in the case under discussion there was excessive bleeding, and one might suppose that with the alteration in the normal hormonal relations, the suppression of the estrogen and the interference with the normal growth of endometrium the patient would have bled from that. The bleeding had lasted for a long time, however. To emphasize the Sertoli cells again, we know that Sertoli cells can form estrogen in dogs, in men and in women, and tumors of this type have been found in all three sources that I have mentioned. I believe, therefore, that this is probably the source of the estrogen formation that this patient had. She had no evidence of masculinization. Teilum,[12] of Copenhagen, has shown that tumors of this type can be estrogen producing. He emphasized, and I think this is something that should be emphasized, that the pathologist should classify the tumors morphologically and not be influenced too much by the clinical story. There has been a tendency, as Teilum points out, for pathologists to classify as a granulosa-cell tumor a lesion with a histologic appearance like this solely because the patient had evidence of estrogen formation. I consider this a very well differentiated arrhenoblastoma, and I suppose in view of the clinical findings that it may have been estrogen producing.

DR. MEIGS: At the time of operation a visitor from Belgium sitting in the stand said to me, "Dr. Meigs, that is an arrhenoblastoma." I said to myself, it cannot be an arrhenoblastoma, for the patient is flowing and has produced plenty of estrogen and has no signs of hirsutism or masculinity.

Since operation three months ago the patient has been very well and has had two normal menstrual periods. She has not become pregnant.

DR. STURGIS: Did you say you did a wedge resection on the other ovary?

DR. MEIGS: Yes; I did.

DR. FENNELL: The other ovary had some thickening of the capsule that was not too striking. There was some lining up of the immature follicles below it; cysts were present, and the cysts were lined by a granulosa and prominent theca layer. The left ovary was similar in the part not involved by tumor.

DR. STURGIS: Would you call it consistent with Stein–Leventhal ovaries?

DR. FENNELL: Yes, but one occasionally sees ovaries from patients who have no hormonal disorder that have the same histologic changes. The pathologist can only say "consistent" with Stein–Leventhal syndrome.

DR. STURGIS: To rescue something from my discussion, may I suggest the possibility that there were two diagnoses — that the nonvirilizing arrhenoblastoma was an incidental finding and that the clinical response was due to the wedge resection rather than removal of the tumor?

DR. FENNELL: Since Dr. Meigs did both procedures, I do not know if we shall ever know definitely which was the main factor here.

DR. JANET W. MCARTHUR: When I saw this patient the features that impressed me were the history of regular periods with cramps during the immediately postmenarcheal years, the profound unhappiness that she had experienced in a succession of foster homes and the limited hormonal therapy that she had received. Like Dr. Sturgis, I took the initial crampy periods to imply normal menstrual function for at least three years after the menarche; however, to my mind this excluded the possibility of "primary" Stein–Leventhal syndrome since usually patients with this disorder never achieve truly regular menstruation. I thought that she had functional uterine bleeding, possibly initiated during the period of emotional distress and insufficiently treated with hormones, and postulated that the palpably enlarged ovary contained a follicular cyst. The culdoscopic observation of apparently characteristic Stein–Leventhal ovaries was a shock, not dispelled until Dr. Meigs found the tumor at operation.

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MEETING OF THE COUNCIL

THE Council of the Massachusetts Medical Society on February 3, 1954, held its stated winter meeting, the longest in recent years. Convening at 10:30 in the morning it did not rise from its feast of reason until 4:00 in the afternoon, barring an intermission for the refreshment of the flesh provided by the late Dr. Cotting.

Another restoration, announced from the chair, was that of the Society's sixth delegate to the American Medical Association; this augmentation was occasioned by the fact that the Society's paid-up membership in the relatively youthful parent organization has again risen to over 5000.

A consideration of the report of the Subcommittee on Mental Health of the Committee on Public Health evoked a discussion relative to the psychiatrist and his hire. In view of the many hours that psychiatrists are not infrequently called on to spend in the treatment of members of physicians' families, the subcommittee had made the recommendation that, whereas psychiatrists should not charge physicians or their families for consultation, if a physician's dependent should require intensive, protracted psychiatric treatment, the patient should be allowed to determine the financial arrangement.

A general discussion brought forth the suggestion that on occasion certain patients of psychiatrists may be incapable of making satisfactory financial arrangements; more to the point was the argument that psychiatrists, as physicians, should operate according to the same rules of etiquette as their more somatic-minded colleagues. Any private arrangements that they make with their patients need not, after all, become an object of parliamentary procedure. This principle prevailed with the Council.

After considerable discussion the Council reaffirmed its financial as well as its spiritual support of the Postgraduate Medical Institute.

Again after considerable discussion the Council accepted the recommendation of the Committee on Finance that the Society "contribute $1000 for the benefit of needy and deserving medical students, preferably in the form of scholarships" to each of the three medical schools of the State. Since it is common knowledge that the medical schools are most urgently in need of unrestricted funds, the Council showed its wisdom in not insisting on the establishment of scholarships, popular as that form of beneficence may be.

By far the most time-consuming discussion of the meeting revolved around a resolution that had been presented by a member of the Middlesex South District Medical Society to that body, and referred by it to the Massachusetts Medical Society without recommendation. The resolution opposed the action of United Community Services of Metropolitan Boston in dropping the New England Hos-

pital from its fund-raising activities, although continuing it as a member of the planning division. This action had been interpreted as a discrimination against women in medicine although abundant evidence had been presented that the matter had had serious, sympathetic and repeated consideration, and that the decision had been based purely on practical and economic factors. Such was the opinion of the Committee on Hospital and Professional Relations, which had recommended that the resolution be not adopted.

The resolution was ably and forcefully upheld by Dr. Susannah Friedman, who argued her point with the eloquence of a Portia. The decision of the Committee was nevertheless upheld.

FINAL SCORE ON 1953

THE general health record of 1953, as determined by the statisticians of the Metropolitan Life Insurance Company, has already been commented on in these columns. Further data on the vital statistics of that eventful year, which has perhaps marked a turning point in man's relations to man, have now been revealed from the same infallible source.

Accidents, according to the Metropolitan Life Insurance Company's indefatigable statisticians, although they reached the grim total of 94,000 fatalities, nevertheless took 2000 fewer lives than in 1952. Further encouragement may be found in the fact that for the first time in four years the number of such deaths decreased from the preceding year's total; this toll, however, is still exceeded only by that of cardiovascular diseases and cancer.

Motor-vehicle accidents, with the needless slaughter of 38,000 persons, remain on about the same level as in 1952; the massacre of 40,000 human beings who ventured on the highways in 1941 has mercifully never since been equaled. The total of 27,500 lives lost as a result of home accidents, although 1500 fewer than in 1952, demonstrates again that domestication in America is but another form of dangerous living. Injuries sustained while the victim was at work took 15,000 lives and present a further argument in favor of a life of ease, provided the unemployed person stays off the highways and away from home.

On the other side of the ledger stands the 1953 birth rate, characterized as a continuation of the greatest baby boom in United States history; not only were 3,950,000 live births recorded, to establish a record, but for the seventh year in succession the number of births exceeded 3,500,000. These advents were at the rate of 25 per 1000 population.

These duly registered hostages of fate have, moreover, the best chance of survival on record, for infant mortality declined during the year to 28 per 1000 live births. This rate represents a decline of 30 per cent from that of 1943, and of more than 50 per cent from that of 1933.

All in all the figures indicate a still increasing life span, with mitigation of many of the hazards that once threatened the years of youthful yearning as well as the period of mature productiveness.

PHYSICIANS OR POLITICIANS?

SEVEN thousand 20-page booklets entitled "What is the Proposed Bricker Amendment to the Constitution?" and published by a "Foundation for Study of Treaty Law" (otherwise unidentified) have been distributed by a public-relations firm in Cleveland. Accompanied by a flyer signed by the President of the American Medical Association urging their distribution among friends of the medical profession, they were recently delivered to the headquarters of the Massachusetts Medical Society by air express.

The booklet contains the full text of the proposed Bricker Amendment, 14 pages of moderately worded argument explaining why it is desirable, and a three-page summary of objections to the Amendment. Since the presidential flyer is marked "Urgent" and contains the advice, "Write or wire your United States senators at once, urging them to support it," this may fairly be regarded as propaganda for the proposed amendment (of which a majority of the councilors of the Massachusetts Medical Society have voted approval).

Is such political propaganda an activity covered by the provisions of the Society's charter? Should physicians express an official interest in legislation

that only potentially (and then indirectly) may possibly affect the practice of medicine?

The booklets have been handed over to the secretaries of the district societies. Perhaps they would appreciate the prayers of the fellows of the Society for guidance regarding what to do with them.

HEART MONTH

FEBRUARY, through a pleasantly exploited sentiment, has become literally the month of hearts. Long dedicated to the adoration of St. Valentine it has been somewhat less erotically appropriated by those who consider the heart only as a muscular organ of greater or less integrity. Its functioning in the service of mankind, imperfect as it often is, has rightly become the object of research and of a gigantic effort directed toward the prevention and treatment of its disturbances. February, therefore, is the month when the heart associations call on us to open our hearts as a preliminary to a similar operation on our checkbooks.

So far as its social and economic implications are concerned, heart disease may be divided into two classes — the infections and congenital defects of the young, and the degenerative diseases of maturer years. The former might be dispensed with entirely to the betterment of mankind, in a physical sense, at least; some sober thought should be given prior to the abolishment of the latter, if that is under consideration.

Perhaps a mere postponement of its eventual triumph over the flesh might be contemplated. Since physical immortality is not yet in view should not this form of heart disease be encouraged to persist, but with a delayed action, on the principle that nature continues to abhor a pathological vacuum? After all, who could wish for a pleasanter slipping of the mortal coil than that of the lord justice of England who died at the age of ninety-four, of a heart attack, having just hooked a salmon?

In the interests of the control of heart disease, therefore, and not of its extinction, may the heart associations — local, regional and national — achieve their goal this month! Each heart that makes its owner give will have its compensation — if not on earth, at least in Heaven.

At Sterling, Mass., Mr. Ezra G. Powers died Jan. 21. The Clinton Courant states that his death — in the opinion of the three intelligent physicians whose attention was called to the case — was caused by disease growing out of the use of water drawn through a lead pipe, against which his attendant physician had repeatedly cautioned him.

Boston M. & S. J. *February 22, 1854*

MASSACHUSETTS MEDICAL SOCIETY

DEATH

BASSOW — George J. Bassow, M.D., of Athol, died on January 16. He was in his seventy-eighth year.

Dr. Bassow received his degree from Baltimore University School of Medicine in 1899. He was a member of the New England Obstetrical and Gynecological Society.

He is survived by his widow and two sons.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The March schedule of the Consultation Clinics for Crippled Children in Massachusetts is as follows:

ORTHOPEDIC CLINIC	DATE	CLINIC CONSULTANT
Salem	March 1	Paul W. Hugenberger, M.D.
Gardner	March 2	Carter R. Rowe, M.D.
Haverhill	March 3	William T. Green, M.D.
Greenfield	March 4	Charles L. Sturdevant, M.D.
Lowell	March 5	Albert H. Brewster, M.D.
Lynn*	March 8	Daniel M. Killoran, M.D., and John J. Crowley, M.D.
Brockton	March 11	George W. Van Gorder, M.D.
Springfield	March 16	James D. Fisher, M.D.
Pittsfield	March 17	Edward J. Coughlin, Jr., M.D.
Fall River	March 22	David S. Grice, M.D.
Hyannis	March 25	Paul L. Norton, M.D.
Worcester	March 26	John W. O'Meara, M.D.

RHEUMATIC-FEVER CLINIC	DATES
North Reading	March 2, 9, 16, 23, 30
Fitchburg	March 3, 10, 17, 24, 31

PLASTIC CLINIC	HELD	CONSULTANT
Eastern Massachusetts	Semi-monthly	Bradford Cannon, M.D.
Western Massachusetts	Monthly	Joseph M. Baker, M.D.

Physicians referring new patients to clinic should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Clinic.

NOTICES

HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the amphitheater, Building D, Harvard Medical School, on March 9, at 8 p.m. The following program will be presented by the Department of Pathology, Harvard Medical School, with Dr. Arthur T. Hertig presiding:

Comparative Histologic and Immunologic Studies on Hypersensitivity of the Serum-Sickness Type. Frederick G. Germuth, Jr., Mary G. Pace and Jack C. Tippett.

The Pathogenesis of Lower-Nephron Nephrosis with Special Reference to the Possible Role of Capillary Thrombosis in Its Etiology. Donald G. McKay, Robert H. Holmes and Robert M. Hardway, III.

The Microbiochemical Approach to Problems in Pathology. Edgar B. Taft and Jesse F. Scott.

Some Histochemical Studies on the Normal and Abnormal Human Endometrium. Arthur T. Hertig, Eleanor C. Adams, Donald G. McKay, Wadi A. Bardawil, Sarah Danziger and Joseph T. Velardo.

NEW ENGLAND CARDIOVASCULAR SOCIETY

A meeting of the New England Cardiovascular Society will be held in Morse Auditorium, Museum of Science, Boston, on March 8 at 8 p.m. The Children's Medical Center and the New England Center Hospital will present the following program:

Children's Medical Center (Dr. Benedict F. Massell, presiding).

Pulmonic Stenosis with Intact Ventricular Septum: A correlation of clinical and physiological data in 50 patients. Drs. Alexander S. Nadas, Benjamin K. Silverman and Walter T. Goodale.

Treatment of Coarctation of the Aorta by the Use of Aortic Homografts. Dr. Robert E. Gross.

Clinical Course of Subcutaneous Nodules in Rheumatic Fever, and Its Significance in Relation to Treatment of Carditis with ACTH and Cortisone. Drs. Benedict F. Massell and Alexander J. MacDonald.

New England Center Hospital (Dr. Samuel Proger, presiding).

Serum Lipids in Atherosclerotic and Normal Subjects as Studied by Paper Electrophoresis. Dr. I. Rosenberg.

The Patient with Coronary Disease as an Operative Risk. Drs. Benjamin Etsten, Daniel C. Weaver, J. B. Friedman and Samuel Proger.

Diamox in the Treatment of Congestive Heart Failure Resulting from Cor Pulmonale. Drs. W. B. Schwartz, Jr., Alexander Leaf and A. S. Relman.

Physicians and medical students are cordially invited.

SOCIETY MEETINGS AND CONFERENCES

FEBRUARY 23. Hampden District Medical Society. Page 224, issue of February 4.

FEBRUARY 23, MARCH 2, 9, 16, APRIL 8 and 20. Boston City Hospital House Officers' Association. Page 265, issue of February 11.

FEBRUARY 23–25. College of Medical Evangelists Alumni Postgraduate Convention. Page 1044, issue of December 17.

FEBRUARY 25. Consultation Clinic for Crippled Children. Page 180, issue of January 28.

FEBRUARY 26 AND 27. New England Diabetes Association. Page 129, issue of January 21.

MARCH 1 and 15, APRIL 5 and 19. Hartford Medical Society. Page 1130, issue of December 31.

MARCH 1–26. Consultation Clinics for Crippled Children. Page 303.

MARCH 3 and APRIL 21. Massachusetts Society for Research in Psychiatry. Page 730, issue of October 29.

MARCH 8. New England Cardiovascular Society. Notice above.

MARCH 9. Harvard Medical Society. Notice above.

MARCH 11–13. American Orthopsychiatric Association. Page 129, issue of January 21.

MARCH 12–MAY 21. Boston Lying-in Hospital Journal Club. Page 38, issue of January 7.

MARCH 15–26. Course in Laboratory Diagnosis of Virus Diseases. Page 1044, issue of December 17.

MARCH 20, APRIL 17 and MAY 15. Massachusetts Hospital School Orthopedic Rounds. Page 265, issue of February 11.

MARCH 22–25. American Academy of General Practice. Page 129, issue of January 21.

MARCH 24. Middlesex East District Medical Society.

MARCH 27 and 28. American Psychosomatic Society. Page 1044, issue of December 17.

MARCH 28. National Gastroenterological Association. Page 265, issue of February 11.

MARCH 31–APRIL 2. American College of Surgeons Sectional Meeting. Page 266, issue of February 11.

APRIL 7. Massachusetts Academy of General Practice. Spring Clinical Assembly, New Bedford.

April 8–11. International Academy of Proctology. Page 130, issue of January 21.

APRIL 9. New England Society of Anesthesiologists. Page 87, issue of January 14.

APRIL 10. American Congress of Physical Medicine. Page 266, issue of February 11.

APRIL 29, 30 and May 1. American Goiter Association. Somerset Hotel, Boston.

MAY 11. Middlesex East District Medical Society Annual Meeting. (Harlow Dinner.)

MAY 12. Essex North District Medical Society Meeting. Andover Country Club, Andover.

MAY 14–16. Fifth Annual International Group of Doctors in Alcoholics Anonymous. Page 1004, issue of December 10.

MAY 14–16. American Academy of Dental Medicine. Page 38, issue of January 7.

MAY 31–JUNE 3. American Urological Association. Page xvii, issue of July 23.

JUNE 17–19. American Geriatrics Society. Page 266, issue of February 11.

JULY 22 and 23. International College of Surgeons Regional Meeting. Page 828, issue of November 12.

JULY 23–29. International Cancer Congress. Page 914, issue of November 26.

SEPTEMBER 7–10. Nineteenth Annual Congress of the United States and Canadian Sections of the International College of Surgeons. Page 828, issue of November 12.

SEPTEMBER 12–15. Second International Congress of Cardiology. Page 44, issue of July 2.

SEPTEMBER 16–18. American Heart Association Annual Scientific Sessions. Page 44, issue of July 2.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, FEBRUARY 25

THURSDAY, FEBRUARY 25

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

*9:00–10:00 a.m. Grand Rounds. Russell Room, House of the Good Samaritan.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.

11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

*12:00 m.–1:00 p.m. Some Related Medical and Ophthalmological Problems. Dr. Howard A. Blazar. Stearns Auditorium, New England Center Hospital.

*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

FRIDAY, FEBRUARY 26

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.

*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.

*4:00–6:00 p.m. X-Ray Conference. Dr. Merrill Sosman. Stearns Auditorium, New England Center Hospital.

*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

SATURDAY, FEBRUARY 27

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:00–9:00 a.m. Anesthesia Conference. Dr. Etsten. Pratt Diagnostic Clinic, New England Center Hospital.

*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.

*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.

*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.

*9:00–10:30 a.m. Surgical Grand Rounds. Dr. Child and staff. Stearns Auditorium, New England Center Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

(Notices concluded on page xxi)